*The Physiology and Treatment of Peptic Ulcer*

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*The present volume is dedicated to*

LESTER R. DRAGSTEDT

*in recognition of his monumental contributions to the field of gastrointestinal physiology and surgery. Each contributor is either a former student or a clinical associate. Over the years each has shared with him some of the points of view which have emerged from their common interests.*

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# *Preface*

The first four chapters of this volume relate to the physiology of gastric secretion and describe experiments selected from a large number designed and conducted by Dr Lester R Dragstedt and some thirty younger associates during the past forty years These experiments have led to a new concept of the pathogenesis of peptic ulcer and a satisfactory explanation of the differences between gastric and duodenal ulcers especially in their response to surgical treatment Chapter 8 presents a brief discussion of the rationale and results of vagotomy and gastroenterostomy as observed at the University of Chicago Clinics over the past fifteen years

Those contributing to the remaining chapters of this volume were selected because of their many years of association with Dr Dragstedt No attempt has been made to reconcile differing points of view especially regarding medical and surgical management of peptic ulcer Where opinion is divided where differences in experience have led to divergent conclusions and emphases the authors have been encouraged to present their own viewpoints Regardless of their individual orientation however all the authors applaud the important contributions made by Lester R Dragstedt and his associates and recognize the significant impact that these have had upon our understanding of the etiology and treatment of peptic ulcer

This monograph was planned without the knowledge and counsel of Dr Dragstedt—for the occasion of his retirement Therefore it has not achieved its fullest potential scope and richness However this is partly compensated for by the use in this book of many drawings from the large collection in Dr Dragstedt s laboratory and the anticipated publication of his own monograph on peptic ulcer

# Contents

# 1 *Peptic Ulcer Studies Concepts, Terminology, and Experimental Methods*

The purpose of this introductory chapter is to provide background material for understanding peptic ulcer studies both clinical and experimental The chapters which follow reflect the particular orientations of the various contributing authors toward that subject It would be illogical and distracting for any of them to depart from a specialized discussion to present a survey of the field the terms used or the methodology Here then for reference as needed is an attempt at basic definitions and general information about the ulcer problem

**Benign peptic ulcer** is a pathologic lesion related to an increase of hydrochloric acid in gastric juice This rise in gastric acidity is usually a manifestation of a physiologic disturbance affecting one or more of the mechanisms which normally regulate gastric secretion In addition there may be other factors which play a role in the genesis of peptic ulcer but which do not normally exert an influence upon gastric secretion

## ACID AND PEPSIN IN THE PATHOGENESIS OF PEPTIC ULCER

The ulcer is a sequela of the digestive action of **pepsin**, but the activity of this enzyme depends upon the **acidity** of gastric juice If the pH is above 4 0 the action of pepsin is largely inhibited maximum activity occurs at about pH 2 0 Little is known as to the mechanism of pepsin production Some believe it to be continuously secreted although it is

influenced by physiologic factors such as those which control the acid content of gastric juice Therefore all forms of treatment designed for patients with peptic ulcer disease are directed either toward neutralization of the excessive acid secretion or toward restriction of the quantity pro duced "no acid no ulcer"

Developments during the past two decades have done much to answer the perennial question Why does not the stomach digest itself? But pres ent knowledge is still insufficient either to prevent ulcer or to insure permanent relief by non surgical means It has been estimated that ap proximately 5 per cent of the total adult population in this country are afflicted with peptic ulcer on one or more occasions during their lifetime Therefore the emphasis on the control of acid in gastric juice has re ceived considerable attention particularly in recent years This subject has engaged the interest of many practicing physicians and surgeons some of whom have made important contributions which either modified older therapeutic measures or provided new potentialities for the control of peptic ulcer

Since the days of Heidenhain (1834–97) and Pavlov (1849–1936) the experimental approach has played an increasingly important part in the study of this disease The dog by means of various surgically constructed **gastric pouches,** has proved particularly useful The pouches enable surgeons and physiologists to simulate if not to duplicate under con trolled laboratory conditions the many clinical variants of peptic ulcer disease and to define *a number of the factors which regulate* gastric se cretion The construction and use of gastric pouches is described in greater detail later in this chapter Indeed their experimental value is such that they are discussed from various aspects in several chapters of this volume

**Uropepsinogen** is generally believed to represent pepsinogen which enters the circulation from the parietal cells of the stomach and thereafter appears in the urine When urine is strongly acidified uropepsinogen is activated to **uropepsin** and peptic activity may be demonstrated Pepsin may also be detected in blood en route to the kidneys Normally the ex cretion is greater in males than females a sex difference that also obtains for the normal gastric secretion of hydrochloric acid This is of interest since the number of male patients with duodenal ulcer exceeds the number of females by a ratio of about 3 to 1

Several workers have demonstrated an increase of uropeptic activity in patients with active duodenal ulcer As might be expected both the free acid content of gastric secretion and the quantity of uropepsin in urine remain elevated in patients whose duodenal ulcers have been healed by medical management if the anti ulcer therapy is discontinued Similarly predictable is the decrease of free acid and uropepsin when patients with

duodenal ulcer are treated by vagotomy or gastric resection In pernicious anemia both free acid and uropepsin are essentially non existent Both are materially reduced in carcinoma of the stomach But both are increased to some extent when patients with intact gastric secretory apparatus are placed on corticoid therapy this will be discussed in a later context

As indicated in the preceding section on pepsin gastric analysis of peptic activity has yielded inconclusive results If the data on uropepsin hold up an increase of uropeptic activity in patients with duodenal ulcer may prove to be very useful clinically

## PHASES OF GASTRIC SECRETION

From the clinical and experimental information gained in recent years it is possible to justify a tentative classification of peptic ulcer according to the physiologic disturbances responsible for its pathogenesis The **vagal or cephalic phase of gastric secretion** is well established There are also strong supporting data to indicate the existence of a hormone **gastrin** liberated by appropriate stimulation of the gastric antrum gastrin production constitutes the **gastric or antral phase** of gastric secretion and is largely independent of the vagal or cephalic phase The **intestinal phase** of gastric secretion concerns still another physiologic mechanism which may contribute to the pathogenesis of peptic ulcer

In addition ulcer may result from disorders in one or more of the endocrine glands either from hyperplasia or from a functioning tumor For example it is known that patients with hyperparathyroid disease those with certain tumors of the adrenal cortex and those who suffer from non insulin bearing tumors of the islet cells of the pancreas have an incidence of peptic ulcer which is much higher than chance alone should allow Unfortunately little is known of the exact relationship of these endocrine diseases to the genesis of ulcer The same uncertainties exist about the modus operandi of gastric physiology insofar as the corticoids may be responsible for Cushing s ulcer Curling s ulcer and the peptic ulcer of stress these also may eventually prove to be related to disturbances in endocrine function

Finally the very recent researches of Dr James Clarke and associates have demonstrated a sharp increase in production of acidic gastric juice following the transposition of the portal vein and the inferior vena cava This observation is of considerable clinical interest for evidence is accumulating which suggests an increase in duodenal ulcer following portacaval anastomosis Meat intoxication which Pavlov noted in the Eck fistula dog (the forerunner of modern portacaval shunting procedures) was subsequently explained by Krebs in 1937 as based on an increase in the con

centration of the blood ammonium ion This suggested to Clarke the possibility that the concentration of ammonium in blood might represent still another factor capable of increasing the secretion of acid gastric juice

Presumably this rise in blood ammonium is postprandial in patients with otherwise normal hepatic function and it is capable of achieving even higher concentrations in patients whose portal circulation has been diverted around the liver or whose severely impaired liver function interferes with the hepatic metabolism of blood ammonium reaching the liver The effect of increased blood ammonium upon gastric secretion is not diminished by vagotomy or by removal of the gastric antrum The latter suggests that the action of blood ammonium as a secretagogue is similar to that of the gastric hormone gastrin

## GASTRIC CONTENTS AND GASTRIC JUICE

Hydrochloric acid once produced appears in two forms **free** and **bound** That portion of acid which combines with hydroxyl (OH) ions or with certain of the protein moieties—the bound acid—does not figure in the genesis of peptic ulcer On the other hand the quantity of free or unbound hydrochloric acid in gastric contents is intimately related to the cause of duodenal ulcer and probably also gastric ulcer (see chaps 4 and 6) Thus it is the free acid which must be counteracted by alkaline secretions or food if acid peptic digestion of the mucosa is to be prevented

Usually the gastric juice collected by nasogastric suction is contaminated with saliva and other oral and pharyngeal secretions as well as by the regurgitant fluids from the duodenum Pure gastric juice is seldom obtained except from the total gastric pouch in the experimental animal and only then if the pouch has been isolated completely from the esophagus and duodenum The oral and duodenal contaminants do not usually interfere significantly with the detection of the free acid in the gastric juice of patients but nevertheless gastric secretion collected under these circumstances is more accurately called **gastric contents** than **pure gastric juice** Unless controls justify the latter the term gastric contents *will be used here*

### METHODS FOR EVALUATING GASTRIC ACIDITY

Any attempt to determine the quantity of hydrochloric acid produced in gastric secretion must be related to some unit of time Obviously the longer the period during which gastric secretions are collected the greater will be the quantity of acid output Moreover the concentration of hydrochloric acid does not always parallel the increase in volume of gastric juices secreted The **twelve-hour, overnight collection** has proven of

great value since it tends to smooth out hourly variations Normal secretion contains between 30 and 50 mEq HCl per liter volume of gastric juice secreted or 18 mEq for the twelve hour fasting state since the total volume of gastric secretion collected in normal controls ranges from 300 to 500 ml for the twelve hour period

In patients with active duodenal ulcer however there is generally a sharp increase in the quantity of HCl produced as well as a rise in the volume of gastric contents collected under the basal conditions of the twelve hour period Dragstedt and his associates in 1949 presented their experience with this method in studying normal individuals and patients with active ulcer disease These findings are shown in Table 1 Had only

TABLE 1

FREE HCL IN GASTRIC CONTENTS
(Twelve Hour Night Secretion)

| Subjects | No. Tested | Volume of Contents (Ml.) | Amount of Free HCl, 12 Hour Collection | | |
|---|---|---|---|---|---|
| | | | C L (Based on 100 Ml Aliquot) | Total Quantity (mEq) | Total Quantity (Mg) |
| *Normals* | | | | | |
| a) Hospital personnel volunteers | 23 | 581 | 31 | 18 | 674 |
| b) Prison volunteers | 23 | 671 | 44 | 30 | 1 080 |
| *Duodenal ulcer patients* | | | | | |
| a) Before vagotomy | 40 | 1 006 | 52 | 55 | 1 980 |
| b) After vagotomy | 40 | 521 | 22 | 11 | 346 |

the **concentration** of hydrochloric acid per 100 ml of gastric juice been used to report results it would have masked to some extent the large increase in **total quantity** of free acid produced the latter is a more relevant index in studying peptic ulcer

Fractional studies have shown that the basal rate of gastric secretion is not necessarily constant from hour to hour justifying the twelve hour measurement however this is not the only acceptable collection period To perform secretory studies on an outpatient basis the **four hour morning collection,** carried out after an overnight fasting period is more practical The results obtained by Levin Kirsner and Palmer using the shorter test period compare favorably with those of the twelve hour test They believe this procedure may be used as a fairly reliable measure of basal secretion when the overnight session is impractical More recently this group has also employed a **one-hour basal test** under similar conditions and has obtained useful information

A **histamine response test** (histalogue) is carried out following the one hour collection. The rate of basal secretion of acid gastric juice is a most useful measurement, and it is possible to gain valuable information by measuring gastric secretion in the normal individual as well as in the ulcer patient under conditions of gastric stimulation such as response to histamine or insulin.

Histamine acts directly upon the parietal cells in the fundus; its action is only slightly affected by vagotomy or antral resection. The influence of insulin, however, is mediated through the vagus nerves so that the results of the insulin test are very *helpful* in appraising the completeness of a vagotomy. Insulin per se has little influence upon the secretion of acid gastric juice unless, following its administration, **hypoglycemia** is allowed to develop. The hypoglycemia elicits an increased rate of gastric secretion. Failure of severe insulin hypoglycemia to produce an early rise in acid gastric juice is reassurance that the vagotomy procedure has been complete. A negative response to the administration of histamine indicates the absence of parietal cells or their inability to respond to this stimulus. The use of insulin and histamine in peptic ulcer research and clinical testing will be discussed further in chapters 2 and 3.

Unfortunately, the rise in total quantity of free hydrochloric acid in the gastric juice of peptic ulcer patients is not compensated for by a commensurate increase in the **alkalinity** of the contents of the duodenal juices (bile and pancreatic secretions and succus entericus). The apparent failure of these alkaline secretions to keep pace quantitatively with increased acidity of gastric contents may explain why the quantity of free acid and not its concentration in gastric juice is more important to the pathogenesis of peptic ulcer; concentration is relative to volume and therefore does not always indicate an increase in the actual quantity of free acid present.

**Gastrin** acts independently of the vagus nerves. Its release is normally stimulated by distention of the antrum or by contact of its mucosal surface with alkaline or neutral foods. Little is known about the chemistry of gastrin, though its hormone like action seems well established physiologically.

The most obvious application of knowledge about gastrin and its antral source of production is the combination of antrectomy with vagotomy in the surgical treatment of duodenal ulcer. If properly performed, these two procedures abolish both the cephalic and the gastric phase of gastric secretion. Equally well established is the increase of gastric secretion sometimes caused by distention of the duodenal stump after subtotal gastrectomy *should some of the antral mucosa remain at the site of duodenal* closure. Similarly, gastric secretion may be augmented in stenosing duodenal ulcer in spite of a complete vagotomy when gastric contents a

cumulate and distend the antrum Such matters are considered at length in chapters 3 4 and 8

## ANATOMIC RELATIONS AND PHYSIOLOGIC RESPONSES

Anatomic demarcation of the gastric cardia its fundus and the gastric antrum are not as clear cut as the surgeon would like these are no more clearly defined than the juncture of jejunum and ileum This is not to imply that these three anatomic subdivisions of the stomach are unreal or that each does not have certain distinct histologic characteristics and physiologic functions However each area merges gradually into the other —grossly as well as histologically In performing a surgical resection of the antrum it is probable that some of the fundic portion of the stomach will be included at the upper end of the resected part and some of the antrum adjacent to the fundus may escape the surgeon

The antral mucosa stops much more abruptly at the proximal end of the divided duodenum But here too the separation is not always clear and sharp Consequently when resecting the stomach or antrum about an inch of the duodenum is generally removed also to safeguard against any antral mucosa being left behind this mucosa does cross into the duodenum occasionally

Of those cells in the gastric mucosa which relate to the pathogenesis of peptic ulcer it is the **acid producing parietal cell** which is most important Parietal and chief cells are greatly reduced in the antral mucosa but abundant in the corpus and in the gastric cardia though somewhat less concentrated In a gastrectomy performed for the treatment of benign peptic ulcer particularly duodenal ulcer the major portion of the corpus must therefore be removed to diminish the quantity of acid produced This is the theoretical basis for both the **Wangensteen sleeve resection,** and the other kinds of operations which attempt to ablate the gastric corpus anastomosing the lower cardia with the antrum These two operative procedures were designed along sound physiologic principles in the hope of preserving more of the gastric reservoir than is possible when the standard **subtotal gastrectomy** is performed in addition the antrum is denervated since the vagus nerves course the surface and intramural areas of the gastric corpus to reach the gastric antrum

The antrum contains some **pepsin producing chief cells** though many fewer than are seen in the corpus or gastric cardia **mucus producing 'goblet' cells** are also distributed throughout the gastric mucosa as are the **argentaffin cells**

We do not know which cells or tissues in the antrum produce gastrin It is unlikely that the goblet or chief cells are responsible these cells are found elsewhere in the gastric mucosa Similarly the argentaffin cells are

widely distributed being found in all portions of the stomach It is possible of course that the goblet chief or argentaffin cells in the antrum are physiologically different from the same types in the corpus and cardia regardless of apparent histologic similarity

## EXPERIMENTAL GASTRIC POUCHES

Since the phases of gastric secretion have been established largely on the basis of experimental observations using pouches some of the distinguishing features of the more important kinds of surgically created gastric pouches should be mentioned *Each has come to be associated with the name of the investigator who devised it* thus using the most simple alternative in nomenclature to describe each pouch otherwise would indeed be a tedious and cumbersome task Four of these preparations and their usefulness to certain studies of gastric secretion are described below Drawings and detailed discussions appear in chapter 2 by Dr Storer

### THE HEIDENHAIN POUCH

First used in 1878 this was the first and is probably the most useful pouch It consists in the complete surgical separation of the left lateral fundic segment of the gastric corpus This pouch is completely detached from its vagal innervation its blood supply is derived primarily from the splenic artery (see Fig 2 p 18) A cannula is introduced into the pouch and led to the outside where secretions from the pouch may be quantitatively collected and measured either as basal secretion or in response to specific stimuli The rest of the stomach retains its vagal innervation and is closed this constitutes the **residual stomach,** which is able to receive and discharge food as before

Heidenhain introduced this pouch primarily for the collection of pure gastric juice but it has also served well as a method for the study of both the cephalic and the gastric phases of secretion When an animal with such a pouch is fed gastric secretion fills the pouch promptly in spite of the complete ablation of vagal innervation to the pouch It was this observation which provided the first suggestion that there is a humoral release from the main stomach occurring in the course of ingesting food and capable of inducing gastric secretion in the denervated fundic pouch Edkins demonstrated in 1906 that gastrin the so called hormone involved is of antral origin

### THE PAVLOV POUCH

This fundic pouch differs from the Heidenhain pouch in that the vagus nerves remain intact The seromuscular layer and its connection with the main stomach are preserved so that the vagal supply to the pouch is not

interrupted Only the mucosa between the pouch and the main stomach is divided The cut edges are then sutured shut creating the isolated pouch and preventing the gastric contents of the main stomach from entering the fundic pouch (see Fig 3 p 18)

The Pavlov pouch was originally devised in 1910 to study the conditioned response It had been found that stimuli which occurred along with those normally accompanying food were sufficient by themselves after a while to cause the animal to expect food an expectation which resulted in increased secretion from the pouch When the vagus nerves were severed the response no longer occurred This was the first experimental demonstration of the cephalic or vagal phase of gastric secretion

THE DRAGSTEDT TOTAL GASTRIC POUCH

This pouch is of the entire stomach with the vagal nerves left intact The vagal fibers are separated from the lower esophagus and lifted to one side so that the esophagus may be transected at its junction with the cardiac portion of the stomach without severance of the vagal nerves to the gastric pouch (see Fig 4 p 20) Continuity of the alimentary tract is re established by anastomosing the cut end of the lower esophagus with the first portion of the duodenum

Thus ingested food passes through the alimentary tract without coming into contact with gastric mucosa the collection of gastric juice is by means of a cannula This pouch has permitted the study of pure gastric juice secreted by the entire stomach in response to food and other stimuli without contamination by food saliva or regurgitated duodenal juices It has been particularly useful in studies on the cephalic and intestinal phases of gastric secretion

THE LIM IVY MCCARTHY POUCH

In this total gastric pouch alimentary continuity is re established as in the Dragstedt pouch This pouch differs from the Dragstedt pouch in that it is denervated the vagus nerves being severed at the level at which the esophagus is transected Its usefulness is primarily in the investigation of the antral and intestinal phases of gastric secretion

It is obvious that the different kinds of pouches and the potential value of each to the study of gastric secretion present almost unlimited research possibilities Total or partial gastric pouches with or without vagal innervation have been constructed to measure the secretory responses of an associated antral pouch **Antral pouches** too have been most useful as will be seen in chapters 3 and 4 Gastric pouches also help to determine the effect of stimulation of the duodenum biliary or pancreatic secretions

on the quantity of acid produced by parts of the stomach and by the total stomach.

## HISTAMINE PROVOKED PEPTIC ULCER

When hypersecretion was found to be one of the major pharmacologic results of histamine stimulation, many investigators began searching for substantial evidence that this might be a natural factor in the pathogenesis of peptic ulcer. In 1939 Code and Varco showed that injections of histamine given daily in beeswax for slow and continuous action produced duodenal ulcer in dogs with a high degree of predictability. The nature of the gastric response consisted in sustained hypersecretion with hyperacidity. This was the first non surgical method for experimentally producing peptic ulcer.

The action of histamine is to stimulate parietal cells directly, bypassing both vagal and antral mechanisms of gastric secretion. It has been useful in demonstrating the functional capacity of parietal cells to produce free HCl. To the same end, histamine has been used to stimulate gastric secretion after vagotomy or antral resection.

In spite of the many failures in trying to relate histamine to spontaneous peptic ulcer in man, the usefulness of the Code Varco procedure in the experimental production of peptic ulcer will be apparent in many of the observations presented in subsequent chapters.

## MUCOSAL RESISTANCE AND PEPTIC ULCER

In the past, considerable attention was given to the concept that peptic ulcer might result from lowered local resistance of the gastric or duodenal mucosa. More recent developments elucidating the physiology of gastric secretion have provided ample explanation for the pathogenesis of peptic ulcer without resorting to this speculation. Even so, theories based on mucosal resistance have not been completely dismissed. **Gastric mucin**, usually considered the lubricant, has received increasing attention as a potential protective mechanism against the corrosive action of acid pepsin. The mucus secretions from Brunner's glands in the duodenum have offered an attractive basis in support of an increased resistance of the duodenal mucosa to peptic digestive action, particularly in the first and second portions of the duodenum.

The **Mann Williamson experiment** seemed at first to point up the great importance of neutralization of acid in gastric juice by the alkaline fluids which entered the duodenum. In such a preparation the duodenal contents are rerouted to enter the lower ileum, diverting the alkaline secretions of the duodenum as well as those entering from the pancreatic and common bile ducts. Recent studies by Dragstedt and others showed

that this anastomosis while diverting the gastric contents to an area unaccustomed to it also stimulated the production of gastric juice to levels above the normal

Two clinical entities exist with which peptic ulcer is fairly frequently associated so that it is not possible to reject completely the theory of reduced local resistance The first is the peptic ulcer occurring in connection with **polycythemia** this complication is believed due to thrombosis of the smaller vessels which impairs viability of tissue in the particular area However this entity too is not without another possible explanation lacking data on gastric secretion in polycythemia one could speculate that this blood dyscrasia stimulates the secretion of acid pepsin

The second entity is the peptic ulcer which often follows the **administration of ACTH or corticoid therapy** Early interpretations suggested *that this ulcer was the result of diminished local tissue resistance* Subsequently there has been some evidence of an increase in acid gastric secretion as one result of ACTH This may be the major factor or at least a possible second component contributing to the pathogenesis of peptic ulceration when it occurs under such therapy However lowered local resistance while a lesser theory cannot yet be dispelled with complete finality

## FREE ACID RELATIONSHIPS OF CLINICAL UNITS AND MILLIEQUIVALENTS

We have seen that gastric acidity under basal conditions is much more meaningfully expressed in terms of the **total output** of free hydrochloric acid than as **concentration** Quantification of gastric acidity demands *accuracy in all details relating to the collection and measurement* These requirements include an uninhibited flow of gastric contents throughout the period of collection pooling and thorough mixing of the total volume collected recording the time over which the collection was made and the measured volume titration for free HCl using a 100 ml aliquot of total collected volume and finally computing the total quantity of free acid contained in the total volume of collected gastric contents

**Gastric acidity** is described as *the number of clinical units of free hydrochloric acid in 100 ml of gastric contents* The **clinical unit** is *that amount of free acid in the 100 ml volume which is neutralized by 1 ml of one tenth normal solution of sodium hydroxide (N 10 NaOH)* Topfer s reagent is used as indicator this is a mixture of 0 5 per cent alcoholic solution of dimethyl amino azobenzene to measure free HCl and a 1 0 per cent solution of phenolphthalein *to indicate total gastric acidity*

Quantitatively the clinical unit in this 100 ml volume is equivalent to 1 ml of N 10 HCl This is the same as 0 1 mEq of HCl since *1 milliequiv*

*alent is that quantity of acid contained in 1 ml of 1 normal solution* For hydrochloric acid 1 normal solution also known as 1 gm equivalent weight per liter equals 36 gm or 36 000 mg Hence

$$1 \text{ mEq of HCl} = \frac{36\ 000}{1\ 000} = 36 \text{ mg} ,$$

and

$$1 \text{ C U} = 3\ 6 \text{ mg} = 0\ 1 \text{ mEq}$$

Hence in terms of concentration

$$1 \text{ C U (based on 100 ml aliquot)} = 1\ 0 \text{ mEq/l}$$

The identical numerical values for concentration and quantity hold only for the 100 ml volume In larger or smaller volumes the concentration or ratio of weight to volume remains constant but the quantity contained will be increased or diminished in accordance with the directions and magnitude of the change in volume These relationships are expressed in Table 2

TABLE 2

QUANTIFICATION OF GASTRIC ACIDITY IN TOTAL COLLECTION OF GASTRIC CONTENTS

| Volume | Concentration (Clinical Unit) | Quantities of Free HCl | |
|---|---|---|---|
| | | mEq | Mg |
| 100 ml aliquot | 36 | 3 60 | 129 6 |
| 1 ml | 36 | 0 036 | 1 296 |
| 1 000 ml | 36 | 36 0 | 1 229 6 |
| 1 650 ml | 36 | 59 4 | 2 011 8 |

Should the gastric acidity relate to a twelve hour 1 650 ml collection of gastric contents which titrates to 36 clinical units of free HCl for the 100 ml aliquot the quantity of acid present is the equivalent of 36 ml of N/10 HCl It is also 36 clinical units of free HCl when expressed as concentration

Certain shortcuts are possible in calculating the quantities of free HCl as shown by the following example

$$36 \text{ C U} \times 1\ 65 \text{ liters} = 59\ 4 \text{ mEq total free HCl}$$

A small amount of the total HCl in gastric secretion is "bound with mucus Normally mucus from the salivary esophageal and gastric glands binds some of the HCl there is also a chemical reaction between free acid and the alkaline regurgitants of the duodenum Most investigators have

found that free HCl comprises 90 per cent or more of the total acid secreted less than 10 per cent of the total secreted appears to be bound

Mucus constitutes a varying percentage of the volume of gastric secretion ranging from 1 per cent to more than 50 per cent in some reports Vineberg (1931) concluded that most gastric mucin derives from the corpus and fundus The quantity produced does not appear to be mate

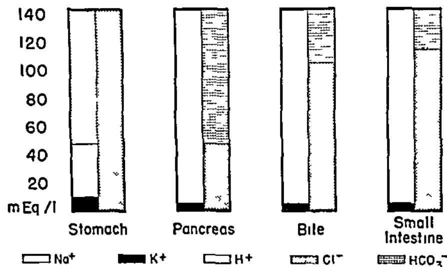



FIG 1—Histographic comparison of the approximate concentrations of electrolyte constituents in the gastric pancreatic biliary and intestinal secretions

rially affected by stimulation at least it is not increased to an extent that it could provide much protective action against augmented secretions of acid pepsin Its chief purpose appears to be as a protection against mechanical thermal and chemical injury

Analyses of normal gastric contents collected under basal conditions are shown in Figure 1 These are normal averages assembled from several reports and therefore not entirely reliable The functions of many of these substances are not well understood nor have they been thoroughly studied

EDWARD H STORER

# 2 The Cephalic Phase of Gastric Secretion

The tasting of appetizing food by a healthy hungry person induces secretion of gastric juice Indeed the sight or smell of food even the thought of good food may stimulate the rate of gastric secretion This increased activity is brought about by a nervous reflex which the vagus nerves carry as efferent impulses to the stomach The resulting secretion is of fairly high acidity and is rich in pepsin This is the **cephalic** or **nervous phase** of the digestive period of gastric secretion The **gastric** and **intestinal phases** comprise the **chemical phase** of the digestive period (See chaps 3 and 4 for detailed discussions of the chemical phase )

In addition to appetite juice mediated by the vagi the gastric glands are intermittently active between meals suggesting that gastric secretion is not solely dependent upon psychic stimuli Increases in gastric secretion can and do occur independently of feeding Variations in tonic activity of the vagi are probably responsible for most of this interdigestive secretion but other factors are obviously involved The drive to ingest food does remain and digestion proceeds after division of the vagus nerves

## HISTORICAL DEVELOPMENTS OF EXPERIMENTAL GASTRIC PHYSIOLOGY

In 1814 Brodie (10) demonstrated that the vagi exercise control over gastric secretion He concluded that "the suppression of the secretion be attributed solely to the division of the vagus nerves and that the secretions of the stomach are *very much under the controul [sic] of the* nervous system" A contemporary John Abercrombie (1) commented "The dependence of the function of digestion upon the influence of the

tenth pair of nerves is among the most beautiful discoveries of modern physiology but nothing of a practical nature has hitherto been deduced from it Nearly a century elapsed however before the mechanisms of gastric secretion were methodically worked out by the great Russian physiologist Pavlov

Active gastric secretion as a response of dogs on seeing food was reported by Bidder and Schmidt (6) in 1852 Richet (67) in 1878 observed a similar response in a man with a gastrostomy on tasting various foods In spite of these and similar observations the role of the vagus nerves remained a contentious one until Pavlov demonstrated experimentally and unequivocally the importance of the vagus nerves in the regulation of gastric secretion He pointed out that most of the German physiologists opposed to his ideas had inadequate data Most of the French physiologists in that day however accepted his views which are well stated in the following quotation taken from a lecture Pavlov (65) delivered in 1897

> The question as to whether the gastric glands have a special secretory innervation is now a very old one and has had an interesting career In this matter physiology stood for a long time in sharp conflict with practical medicine Physicians bringing forward their observations in proof had long answered the question in the affirmative and looked upon the existence of secretory nerves to the stomach as undoubted Physiologists on the other hand had fruitlessly endeavoured for decades to arrive at definite results upon this question This is a striking but by no means isolated instance where the physician gives a more correct verdict concerning physiological processes than the physiologist himself

Pavlov was able to study gastric physiology better than his predecessors because of his unique ability to modify and perfect existing experimental technics for observing gastric secretory function This is well illustrated by the gastric fistula dog Earlier stimulated by Beaumont s observations on his patient with traumatic gastric fistula the Russian Bassov (4) in 1842 and independently the Frenchman Blondlot (7) in 1843 had made gastric fistulae surgically in the dog Many other workers subsequently used this as a method for investigation of gastric secretion and digestion Their early efforts were not particularly successful the juice they were able to collect was contaminated by food saliva and duodenal regurgitants Moreover the gastrostomy tube was frequently plugged with food making continuous collections of gastric contents impossible

In 1889 Pavlov (65) added a cutaneous esophagostomy (Fig 1) to the gastric fistula The dog ate but the food never reached its stomach Instead it left the alimentary tract through a fistula created in the upper segment of the divided esophagus Thus Pavlov s innovation—the basis of

the procedure called **sham feeding**—enabled him to collect gastric juice from the stomach during actual feeding but without the contamination of food or saliva This was an important advance His physiologic preparation also gave conclusive evidence that the response did not depend on the gastric mucosa being stimulated by contact with food

Aside from his excellence as a physiologist and his technical skill as a surgeon Pavlov was an impressive showman He often demonstrated his experimental observations before his students and colleagues The following quotation is from a lecture given before the Society of Russian Physicians it showed conclusively the role of the vagus nerves in gastric secretion by making dramatic use of an actual sham feeding setup

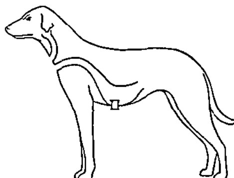


FIG 1—Schematic representation of Pavlov s esophagostomy gastrostomy preparation (From B P Babkin *Secretory Mechanism of the Digestive Glands* 2d ed 1950 Reproduced by permission of the author and Paul B Hoeber Inc )

We have here before us a dog which has an ordinary gastric fistula with metallic cannula and has had its esophagus divided as well so that the mouth is cut off from all communication with the cavity of the stomach at the time of making the gastric fistula the right vagus nerve was divided below its recurrent laryngeal and cardiac branches

I give the dog food The animal eats greedily but the whole of the food swallowed comes out again at the esophageal opening in the neck After feeding in this way (which for shortness we will henceforth name sham feeding ) for five minutes perfectly pure gastric juice makes its appearance at the fistula the stream steadily becomes greater and greater and now five minutes after the commencement of secretion we have already 20 cc of juice The meaning of this experiment is clear It is obvious that the effect of the feeding is transmitted by nervous channels to the gastric glands

About three hours before the present lecture I prepared the left vagus free in the neck passing a loop of thread round the nerve but not dividing it I now pull gently on the thread to draw the nerve outwards and sever it with a sharp snip of the scissors At present the pulmonary and abdominal vagi on both sides are paralyzed while on the right side the laryngeal and cardiac fibres are intact

There are even no symptoms of cardiac or laryngeal distress the usual causes of danger to the animal after complete division of the cervical vagi on the two sides We again offer the dog food to eat which it eats with increasing greed for five ten fifteen minutes but in sharp contrast to the previous sham feeding we do not see a single drop of juice flowing from the stomach We may feed the dog as long as we wish and repeat our experiment in the next few days as often as we desire but never again shall we see a secretion of gastric juice in this animal as a result of sham feeding [65]

While Pavlov recognized that the esophagostomy gastric fistula animals afforded a means of obtaining pure gastric juice no insight into the function of the stomach during digestion could be gained from this preparation He solved this problem with the **Pavlov gastric pouch** an ingenious surgical modification of an existing experimental technic which guaranteed a "continuance of normal gastric digestion side by side with a quantitative collection of perfectly pure juice" (65) It was based on the work of Thiery (75) who had isolated a segment of the intestine formed it into a cul de sac and sewed its open end into the abdominal wound Gastro intestinal continuity was re established by an end to end anastomosis This allowed him to collect pure succus entericus while digestion was going on in the main portion of the intestine

Heidenhain (39) adapted the Thiery cul de sac principle to the stomach and fashioned a pouch from the cardiac end of the stomach which poured its secretions externally (Fig 2) According to Babkin (2) Pavlov became familiar with this type of pouch in 1877 when he worked during that summer in Heidenhain s laboratory in Breslau The vagal innervation of the pouch had been interrupted but the remainder of the stomach had its vagal nerves intact When such an animal ate the food in the main stomach caused a secretion of clear juice from the pouch Since the Heidenhain pouch was isolated from the remainder of the stomach food which entered the stomach did not enter the pouch Pavlov objected to the drawing of conclusions from the Heidenhain pouch as representing the normal function of the stomach because he felt it most important that the nervous connections to the isolated pouch be maintained if the normal responses were to be duplicated experimentally All vagal branches to the Heidenhain pouch were divided in the course of its preparation for the pouch was surgically separated from the main stomach

Pavlov retained some vagal innervation to the greater curvature of the stomach which he used as the pouch by leaving a portion of the sero muscular layer intact The cavity of the main stomach was separated from that of the pouch by suturing the mucosal layer between these two gastric segments thus creating an innervated pouch while retaining the main stomach (Fig 3)

Duodenum

Heidenhain pouch

FIG 2 —The Heidenhain pouch as modified by Dragstedt Note that this is necessarily a denervated pouch (From Woodward Lyon Landor and Dragstedt 1954 *Gastroenterology* **27** 766 )

1

Esoph

B

A

C

C

2

S

V

S

A

A

FIG 3 —The Pavlov pouch as originally described *Sketch 1* site of the operation *A–B* line of incision *C* region used to form pouch *Sketch 2* finished preparation *S* Pavlov pouch *V* stomach cavity *A A* abdominal wall (From I P Pavlov *The Work of the Digestive Glands* 1902 Courtesy of Chas Griffin & Co London )

When animals with Pavlov pouches were fed augmentation of gastric secretion from the pouch occurred within five minutes Thereafter it increased rapidly reaching its peak in approximately fifteen minutes It then began to subside fairly rapidly but before the basal secretory volume was reached a second rise was noted Not only was its level higher than that of the initial rise but the augmented rate of secretion persisted for several hours The first of these two secretory responses was the result of **vagal stimulation,** marking the **cephalic** phase of secretion The second or latent rise was due to the **local stimulation of food** entering the stomach and intestines and this we now know as manifestation of the **gastric** and **intestinal** phases they are generally considered as the chemical phases of gastric secretion (chaps 3 and 4) Pavlov not only investigated the chemical phase of secretion he anticipated Edkins work on gastrin by several years He wrote in 1897 Digestive products are known not to be absorbed from the stomach to any extent but it may be that by their agency other substances with stimulating properties are formed in its lining cells from whence they are taken into the blood stream and become distributed to the gastric glands" (65)

Although the Pavlov pouch was of great value in working out many details about the physiology of gastric secretion its value was severely limited because of its meager vagal supply This important defect in the Pavlov preparation was recognized by Dragstedt (25) who devised a total stomach pouch in which vagal innervation as well as blood supply remained completely intact (Fig 4) Fremont (35) is sometimes credited with making the first total pouch but his one brief inadequate report in 1895 did little to support this claim

By use of a threaded cannula to which a balloon was attached Dragstedt was able to collect all gastric secretions The Dragstedt innervated pouch secretes from 600 to 1 200 cc of gastric juice daily If the vagi to such a pouch are divided as in the denervated total Lim Ivy McCarthy pouch (54) the daily secretion is sharply curtailed generally to about 25 per cent of that observed in animals with the Dragstedt pouch in which the vagi are preserved (28) This marked difference in the daily secretion is an indication of the importance of the role played by vagus nerves

## DEMONSTRATION OF VAGAL SECRETION IN MAN

### ACCIDENTAL GASTRIC FISTULA

The first serious use of a human gastric fistula patient to study gastric physiology was by Captain William Beaumont (5) a surgeon in the United States Army Alexis St Martin a young French Canadian had received a shotgun wound at close range a massive wound of the lower left chest including the lung diaphragm and stomach It healed slowly

under Beaumont's care leaving however an opening into the stomach about two and one half inches in diameter Captain Beaumont recognized the unique opportunity which St Martin's misfortune provided for direct observations of gastric physiology in man and he was able to record many important facts from 1825 through 1833 which remain unchallenged to this day Beaumont recorded only a few observations about the mecha

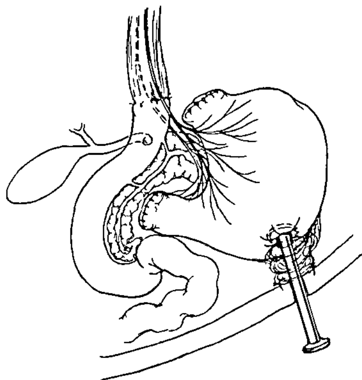


Fig 4 —The Dragstedt total gastric pouch Note that the entire vagal supply is preserved (From Dragstedt Woodward Neal Harper and Storer 1950 *Arch Surg* 60 1 )

nisms and nature of gastric secretion per se his major interests centered upon gastric digestion He concluded that gastric juice "is never found free in the gastric cavity but it is always excited to discharge itself by the introduction of food or other irritants It is of course possible that St Martin had little or no "appetite juice and little of the interdigestive secretion that sometimes occurs in persons with "normal intact digestive tracts

Carlson (13) in 1916 reported extensive studies on a second Alexis St Martin" Mr V was a twenty seven year old man who had accidentally drunk a strong solution of caustic soda at the age of eleven years As a

result the esophagus was completely closed by cicatricial tissue and a permanent gastric fistula was created. Although Carlson was principally interested in hunger and gastric motility he made extensive observations of Mr V's gastric secretion. When this man sat down to meals he "ate" ordinary food but instead of being swallowed after being masticated it was placed in a syringe for introduction into the stomach through the gastric fistula. This unusual method of eating made possible the evaluation of the cephalic phase of gastric secretion in man. Carlson observed that when the patient was allowed to see or smell food there was little evidence of an augmentation of gastric secretion, but if the patient chewed palatable food moderate increases in the amounts of acid juice occurred, the rate

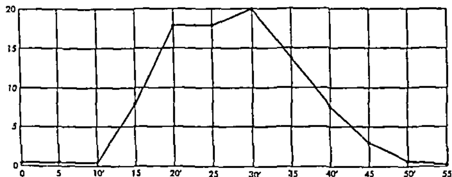



FIG 5.—Typical curve of secretion of gastric juice of Mr V on mastication of palatable food for 20 minutes. The gastric juice was collected at 5-minute intervals for 55 minutes. The rise in the secretion rate during the last 5 minutes of mastication is due to chewing the dessert (fruit). (From Carlson 13.)

of secretion being directly proportional to the palatability of the food (Fig 5). Carlson concluded that Pavlov overestimated the importance of the "appetite juice" in gastric digestion.

Pavlov (65) believed that about 40 per cent of the gastric response to feeding could be attributed to vagal stimulation and thus to the cephalic phase. Although Carlson did not assign a definite figure to the nervous phase his data indicated that about 20 per cent of the total digestive response in this patient was from vagal stimulation.

SHAM FEEDING

Schule (69) in 1897 introduced the technic for obtaining "appetite juice" by gastric intubation and aspiration while the patient chewed a standard meal, expectorating instead of swallowing it. This procedure seems scarcely physiological since it is psychologically repulsive, but it yielded positive results in a surprisingly high percentage of the studies made. This

method of sham feeding has been used successfully as one of the potential measures to test the completeness of vagus section when the operation is employed in the treatment of duodenal ulcer (15).

Sham feeding has never attained much popularity as a clinical method of stimulating the vagi however since its results are not as reliable as other methods. The insulin test detailed below is a simple reliable and effective clinical method of vagal stimulation which circumvents many of the inadequacies that characterize the sham feeding procedure.

THE INSULIN TEST

Hypoglycemia following insulin administration augments both motor and secretory activity of the stomach by stimulating the vagal centers in the brain. The motor effects were noted in animals by Bulatao and Carlson (11) shortly after the discovery of insulin. The secretory effects of insulin were demonstrated in the dog by Collazo and Dobreff (17) in 1924; a year later Detre and Sivo (21) reported that the same response could be elicited in man. These findings have since been confirmed and extended by numerous investigators.

It is the **hypoglycemia**, and not the insulin as such that is responsible for vagal stimulation. This can be demonstrated by administering glucose or epinephrine at the time insulin is given. Hypoglycemia is thereby prevented and gastric secretion remains unchanged (3). If hypoglycemia is allowed to develop after insulin administration the usual response is a rapid rise in the rate and volume of gastric secretion. This response however is abolished when both vagi are sectioned indicating that the action of hypoglycemia is central and not one of direct action upon the gastric glands. Evidence that the vagal centers in the brain are the site of the stimulation created by the hypoglycemia was furnished by an experiment by LaBarre and Cespedes (47). They were able to stimulate gastric secretion in a dog whose brain remained connected to the trunk by the vagus nerves alone and whose head received blood by cross transfusion from a dog made hypoglycemic with insulin.

The magnitude of the gastric response to insulin hypoglycemia is not directly proportional to the extent of the hypoglycemia—mild hypoglycemia *does not yield a small response (46) Gastric secretion in the non* diabetic is stimulated only when the blood sugar drops below about 55 mgm per cent. A further reduction in blood sugar does not further increase the gastric secretory response. The augmented secretions begin as the blood sugar drops below the 55 mgm per cent threshold level; the level of secretion begins to return to normal as the level of the blood sugar again approaches normal. The secretory response lags behind that of the blood sugar however so that the curves of each cannot be superim

posed with reference to time (Fig 6) A delayed response to hypoglycemia has been observed by Moore (60) in man and by Porter Movius and French (66) in the monkey These latter workers suggest that the delayed response is mediated via the adrenal glands since it is abolished by adrenalectomy but unchanged by vagotomy Further studies are needed to elucidate the adrenal relationship to gastric secretion thus far others have been unable to reproduce these reported findings

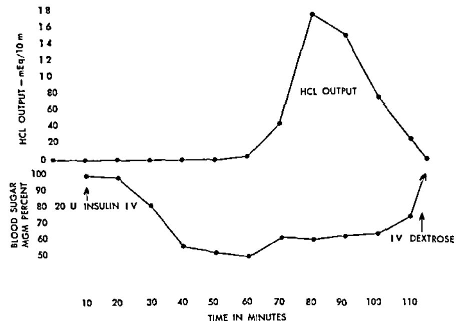



Fig 6 —The gastric secretory response to insulin hypoglycemia

Only a few segments of the vagus nerves to the stomach need be intact to produce an unequivocal positive secretory response to hypoglycemia The insulin test therefore cannot be used as a quantitative measure of vagal innervation (46) For example an animal with a Pavlov pouch whose residual vagal supply is known to be anatomically meager (45) will often display a substantial response to insulin hypoglycemia

## THE INTERDIGESTIVE PHASE OF GASTRIC SECRETION AND METHODS FOR STUDY OF GASTRIC ACIDITY

It has been repeatedly demonstrated that there is a basal gastric secretion in man and higher animals which is independent of the usual digestive stimuli This basal secretion may or may not be continuous it may be

phasic or intermittent. This view was rather slow to be accepted, principally because of the great prestige of Pavlov. Pavlov and his pupil Babkin maintained that the secretory activity of the gastric glands was quiescent between meals and that any acid secretion during this interdigestive period was due to conditioned reflexes.

Although the vagi do appear to play a very prominent role in the interdigestive phase of secretion, there are other contributory factors; sectioning of both vagus nerves does not abolish interdigestive secretion (26), although vagotomy does reduce its volume. That the gastric glands can function in the absence of the usual stimuli, though at a lower than usual level, was demonstrated in the following animal experiments. When a pouch of gastric mucosa is autotransplanted to the subcutaneous tissues and thus devoid of all extrinsic nerve supply, interdigestive secretion of acid continues (42). In another study Davenport (20) showed that the resected stomach of the mouse will secrete acid when suspended in phosphate buffer in a Warburg flask without other kinds of secretory stimulants. The conclusion that there is an intrinsic activity of the parietal cells seems amply justified from such observations alone. This intrinsic activity is of considerable theoretical interest, although it appears of little consequence when considering the total interdigestive secretion, for its volume comprises a very small proportion of the total gastric secretions.

FASTING SECRETION

Studies on the fasting secretion in man have been conducted as overnight collections so as not to inconvenience the patient. The subject is generally *fed a liquid meal about 5:00 P.M.; the observation period of fasting is begun* about 9:00 P.M. and continued for twelve hours. Several methods of assessing production of hydrochloric acid have been used, but none is without *certain objections. Some workers have aspirated* hourly samples of gastric juice via the stomach tube, testing the fluid for free acidity by titration with base, often considering only the **concentration** of free acid, giving no information about the **quantity** of free acid produced (see p. 5, chap. 1). Others have applied continuous suction to an indwelling nasogastric tube. This technic yields more valid and useful information on secretory activity, since the concentration of free acid (units per volume) and its quantity can be determined simultaneously. However, the contact of free acid with the antrum and the duodenum normally inhibits further acid production. Therefore, when gastric contents are continuously removed by aspiration, the inhibiting factor of free acid in the antrum and duodenum is commensurately reduced; consequently, the possibility exists that continuous aspiration may enable the stomach to produce more acid under basal *conditions than would ordinarily obtain*. To obviate this

objection a third method of gastric aspiration has been devised The stomach is completely aspirated and an aliquot of the aspirate used for titration the remainder of the aspirate is reintroduced into the stomach via the gastric tube In this way only a small quantity of acid produced is removed from the stomach so that the major portion of the acid gastric contents can exert its normal inhibitory effect upon the antrum and duodenum To what extent intermittent aspiration and return of gastric contents represents an improvement over continuous aspiration is not known aside from the theoretical advantages mentioned above Using this intermittent procedure for aspiration one cannot measure accurately the total volume secreted because between each aspiration unknown amounts of gastric juice obviously pass through the pylorus and into the duodenum on the other hand if gastric retention is present this technic may simply measure it over and over again by using essentially the same gastric contents

Still another objection to some studies of gastric secretion is the choice of "normal controls The frustrations and anxieties of medical students and penitentiary inmates and the usual controls are probably abnormal even for our harried and frustrated twentieth century mode of life Levin Kirsner Palmer and Butler (50) studied gastric secretion in twenty one males and twelve females all healthy adults They found no instance of anacidity during the twelve hour overnight collections The volume of juice ranged from 148 ml to 1 188 ml averaging 581 ml In the males of the group the average twelve hour collection was 643 ml it was slightly less for females averaging 460 ml Free acid (concentration or quantity) ranged from 1 to 60 mEq/l with an average of 29 mEq/l with no significant sex difference It was also shown that this secretion was not due to the presence of food in the intestine the twelve hour secretion was the same whether collections were started twenty eight hours after eating or only four hours after the last meal (48) Hoelzel (41) found free acid in the gastric contents collected throughout a forty day period of fasting If there remain any doubts about the evidence in support of an interdigestive secretion the Hoelzel observations should dispel them

Levin Kirsner and Palmer (52) and Stein and Meyer (71) have found the one hour aspiration as accurate a measure of fasting acid secretion as the twelve hour overnight test Multiplication of the results of the one hour collection by twelve gives a figure which corresponds well they report with the total collection of the twelve hour period If further testing confirms this the procedure should moderate many of the criticisms to which other methods are subjected The one hour basal study can easily be done in the physician s office or the outpatient clinic the twelve hour study must be done under hospital conditions and necessitates frequent

attention during this period to make sure that the method of aspiration is continuously operating and not interrupted by plugging of the tube or it dislodgment Actually the nasogastric tube should be placed under fluoroscopic control to be certain it is in the stomach

## INTERRELATION OF CEPHALIC AND GASTRIC PHASES OF SECRETION

Straaten (73) postulated in 1933 that the cephalic phase of acid secretion is mediated by release of gastrin from the antrum His views were extended by Uvnas (79) and Linde (55) According to this hypothesis the vagal or cephalic phase cannot operate in the absence of the antrum This hypothesis was disproved by the following observations

First there was no augmentation of secretion in a Heidenhain pouch when the vagus nerves were stimulated by insulin hypoglycemia although a copious secretion of acid was noted in the main stomach (43) If gastrin was released by the vagal stimulation it would be carried to the Heidenhain pouch via the circulation and increase the volume of secretion in this denervated pouch as well as in the body of the stomach

Second when similar studies were carried out on the Dragstedt pouch in which the vagus nerves remained intact the total twenty four hour pouch secretion was shown to be normal by Dragstedt *et al* (31) Similarly the secretory response to insulin hypoglycemia was found to be normal The antrum was then resected and the observations repeated They found that the copious daily secretion continued and that the response to insulin remained positive although both responses were somewhat diminished As a third stage in this procedure the vagal innervation of the pouch was ablated by vagotomy The twenty four hour output of acid secretion was greatly reduced The response to insulin hypoglycemia was abolished indicating that the vagi could and had been functioning in the absence of the antrum

A brief moment of reflection is sufficient to convince any experienced surgeon that the vagi can function all too well without the antrum What a grand situation it would be if resection of the antrum alone would *abolish the cephalic phase in the ulcer patient! If this were true post* gastrectomy marginal ulcers would be almost non existent Dragstedt *et al* (31) found the insulin test to be positive in each of eight cases of marginal ulcer which had developed after gastric resection Obviously the vagi continue to function and to stimulate gastric secretion unless they are divided or the total parietal cell portion of the stomach is removed in the course of resection

Although it is clear that the cephalic phase mediated through the vagus nerves can function to stimulate gastric secretion without the antrum

these experimental observations do not answer this question Is it possible that the cephalic phase does not operate to its fullest extent without the *co operation of the antrum? Perhaps the role of the antrum is facultative* rather than obligatory insofar as the cephalic phase of gastric secretion is concerned Studies have been reported which indicate that this may be true Certain of Linde s experiments (55) suggest this possibility but they were like those of Uvnas (79) in one unfortunate respect the experiments of both were acute and carried out on anesthetized animals with vagal stimulation accomplished with a condenser discharge Their methods created certain complications as well as uncertainty in interpretation of the results observed

Noring (61 62) studied the nocturnal secretions and the sham feeding response in ulcer patients before and after partial gastrectomy He found considerable reduction in acid after the operation both in the overnight secretion measurements and in secretions following sham feedings He recognized the difficulties of obtaining a valid collection of the gastric secretions in the presence of a gastrojejunostomy but felt justified in this conclusion "It seems most likely that the resected part has been a link in the processes which elicit the cephalic secretion"

Dragstedt s work cited above might also be considered as evidence that the antrum contributes in some way to the cephalic phase of gastric acid secretion Dogs with otherwise total pouches retaining vagal innervation displayed a 23 per cent average reduction in the quantity of acid secretions collected after the antrum was removed Antrum resection also reduced the quantitative secretory response to hypoglycemia by an average of 41 per cent

Thus the observations on decreased gastric response to vagal stimuli after antrum resection may indicate that there is a specific co operative function of the antrum in the cephalic phase But this is not necessarily the case It could mean that there has been a general non specific decrease in sensitivity or responsiveness of the parietal cells to any stimulus as a result of the antrum resection There is some evidence to support this hypothesis

Farmer *et al* (33) studied the gastric secretory response to stimulation before and after partial gastrectomy which included the antrum They found that the insulin response was reduced by 79 per cent and the response to histamine was diminished by 85 per cent This would appear to be strong evidence for the view that removal of the antrum decreases the responsiveness of the cell If the antrum were playing a specific role in the cephalic phase the insulin response should be depressed to a much greater degree than the histamine response However following partial gastrectomy there is a substantial reduction in the number of parietal cells

A similar general decrease in responsiveness to any stimulus can also be demonstrated after vagotomy It has been shown repeatedly that the parietal cell response to a given stimulus is decreased by vagotomy This is true in both man and animals and holds for all the usual methods of stimulation test meals caffeine alcohol and histamine The decreased response to histamine after vagotomy is particularly significant though not readily explained since histamine is thought to act directly upon the parietal cell

Therefore it seems that cholinergic and hormonal stimuli acting upon the parietal cell may elicit a summation of the responses which the individual stimuli might evoke if given separately It is not necessary to postulate a specific co operative effect of vagal and antral stimuli to explain observed phenomena

## PATHOLOGIC PHYSIOLOGY OF THE CEPHALIC PHASE (VAGAL INNERVATION)

The preceding portions of this chapter have elaborated the physiologic functions of the vagal nerves in the control of gastric secretion The pathologic aspects as they pertain to benign peptic ulcer of the duodenum and gastrojejunal stoma will now be considered the role of gastric acidity in peptic ulcer the secretory findings in the ulcer patient and the role of the vagi in the control of gastric acidity in the ulcer patient

### THE ROLE OF GASTRIC ACIDITY IN PEPTIC ULCERATION

Although other factors may contribute to peptic ulcer a relatively high gastric acidity is the *sine qua non* for its genesis perpetuation or recurrence Medical and surgical procedures currently used in the treatment of *peptic ulcer are designed to neutralize the acid gastric juice or to decrease* its production The success of treatment is directly proportional to the extent to which the gastric acidity is decreased

The role of acid gastric juice in ulcer production has been demonstrated many times and in many ways in the experimental animal many of these closely resemble clinical cases of peptic ulcer Dragstedt and Vaughn (24) implanted segments of small and large bowel as well as the intact spleen kidney or pancreas into defects in the gastric wall of dogs to determine if the organs would be digested when bathed in gastric juice If the blood supply of the implant was not injured the implant remained undigested and was eventually covered with a thin layer of gastric mucosa *But if such implants were made in the wall of an accessory gastric pouch* the implant was promptly digested and death from hemorrhage or perforation rapidly ensued (22 58) The usual gastric content consists of a mixture of swallowed food and saliva regurgitated duodenal content alka

line gastric mucus secretions as well as acid pepsin from the gastric glands The secretion from an accessory stomach pouch consists almost entirely of the acid pepsin secretions diluted and neutralized only by mucus in contrast to gastric contents (see p 4) Pure gastric juice high in acidity has a marked corrosive action on living tissue while the normal gastric content low in acidity is relatively inert

Histamine was demonstrated to be a powerful stimulant of gastric acid secretion by Popielski in 1920 but his method did not yield reproducible results in the production of peptic ulceration in the duodenum or stomach However in 1940 Code and Varco (16) incorporated histamine in bees wax for slow but continuous release and thereby produced in dogs a sustained hypersecretion of highly acid gastric juice from Heidenhain pouches this hypersecretion lasted for many hours They found that daily intramuscular implantation of the histamine beeswax regularly produced peptic ulcer in a wide variety of experimental animals (38) Though most observers held that the corrosive action of the greatly augmented acid secretion was the mechanism responsible for the ulceration some believed that the vasodynamic and angiotoxic effects of histamine were the basic factors responsible The latter view was disproven when it was demonstrated that anti histaminic agents do not protect against histamine provoked ulcers (36) It is fairly well established that the more effective anti histamine agents block all known effects except the histamine stimulation of the parietal cells

If hydrochloric acid is important to the genesis of peptic ulcer then its intragastric instillation should regularly produce ulcers Such experiments met with varied success until the well designed studies of Cummins Grossman and Ivy (18) They found that continuous instillation of 0 1 normal HCl (N/10) produced duodenal ulcers in dogs only when the pH of the blood of these animals fell to about pH 6 9 When the normal blood pH value of 7 4 was maintained with the intravenous administration of sodium bicarbonate administration of 0 1 normal HCl did not produce ulcers However if the concentration of acid was raised to 0 15 normal then ulcers were produced in spite of the maintenance of normal acid base balance The concentration of pure parietal cell secretion is said to be 0 167 normal HCl

## GASTRIC SECRETION IN PATIENTS WITH DUODENAL ULCER

Common to all methods described for producing chronic peptic ulcers experimentally has been the increased production of acid gastric juice As a matter of fact increasing the acid factor is the only method devised to date for experimentally producing ulcers which resemble benign chronic peptic ulcers as seen in man

Nearly all patients with duodenal ulcer secrete significantly more HCl than do normals Some investigators have found that the **free acid concentration** of the ulcer patient s secretion is not much higher than that of normals for there is considerable overlap of the high acidity normal and the low acidity ulcer patient A difference in the secretions which is more striking is seen in the **volume** of secretion produced and therefore the **total free acid**, using this measure the results obtained from normals show little similarity to those from the ulcer patients Therefore to evaluate gastric secretion in the ulcer patient both the **acidity** and the **volume** of secretion must be considered Multiplying the volume in liters by the milliequivalents of HCl per liter (the free acidity or "clinical units") gives the total amount of acid produced expressed in milliequivalents If one compares the total acid output of the ulcer patient with the total acid output of healthy controls it is clearly evident that nearly all ulcer patients secrete significantly more acid gastric juice than do the normal controls This holds both for tests by stimulation and those which measure secretion during the interdigestive or basal period There is very little overlap between normals and ulcer patients (see p 11)

In a study of acid gastric secretion referred to earlier which Farmer *et al* (33) carried out on ten normal individuals forty one patients with duodenal ulcers and twelve patients with gastrojejunal ulcer the fasting secretion and also the responses to insulin histamine and beef broth were greater in the two groups with ulcer disease than in the controls The findings of others for the individual tests were confirmed but the particular value of this study is that it compares in the same subject the gastric response to a potent neurogenic stimulus (insulin) a potent chemical stimulus (histamine) a physiological chemical stimulus (beef broth) all of which are exogenous stimuli In addition they were able to assemble data relative to the interdigestive secretion for each subject in these groups comprising the study Their results are shown graphically in Figure 7 The quantity of acid in the gastric contents of patients with duodenal ulcer or gastrojejunal ulcer was significantly greater following all forms of stimulation The most striking difference however is seen in the basal or interdigestive phase of secretion confirming and extending the report of Dragstedt *et al* (29) and Levin *et al* (51) Dragstedt found that eighty one normal subjects secreted an average of 551 ml with an average free acidity of 33 mEq/l a total overnight output of 18 mEq HCl One hundred and thirty five patients with chronic duodenal ulcer secreted an average of 1 085 ml with an average free acidity of 52 mEq/l —a total acid output of 60 mEq Levin s results were almost identical 17 8 mEq compared to 61 mEq In summing up the difference between the normal and the ulcer patients Dragstedt (23) wrote as follows

In normal man the secretion of gastric juice in the intervals between meals when there is no food in the stomach or upper intestines falls off to a small quantity that can be buffered by the saliva pyloric mucus and the regurgitated duodenal secretions The chief secretory abnormality in ulcer patients lies not in the production of more normal juice in response to the usual stimuli although there is some evidence that this occurs but rather in the secretion of abnormally large amounts of gastric juice in the intervals between meals particularly at night when the stomach is empty and there is no obvious stimulant The accumulation in the stomach of considerable amounts of such relatively pure fundic secretion obviously provides in man the counterpart of those experiments in animals where ulcers inevitably develop and become progressive

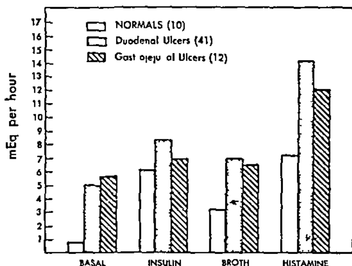



FIG 7 —Graphic demonstration of the marked gastric hypersecretion found in patients with duodenal and stomal ulcers (Courtesy Farmer Howe Powell and Smithwick 33 )

Most have found that male controls have a higher acid output during basal conditions as well as in response to stimulation than do female controls under similar conditions This same relationship holds for the greater secretory patterns obtained in male patients with peptic ulcer than in females with this disease This higher acid output in the male is of considerable interest in view of the fact that males with duodenal ulcers greatly outnumber females with this affliction

The preponderance of the existing evidence indicates that duodenal and gastrojejunal peptic ulceration is characterized by a hypersecretion of acid although the nature of the hypersecretion is probably not entirely identical Does this hypersecretion exist prior to the ulcer and will it continue after the ulcer is healed? Or does an ulcer patient have a normal

gastric secretion until some situation befalls him which causes an increased secretion of acid which in turn causes an ulcer? Or is it the presence of an active ulcer that causes the hypersecretion? These are questions of great practical significance to say nothing of their theoretical importance. Unfortunately there are too little data at present to provide the unequivocal answers necessary to justify even reasonable speculation.

The evidence available relates principally to gastric secretion after healing of the ulcer. The response to alcohol, histamine and caffeine is unchanged; there is no significant difference after healing—the hypersecretion continues (42). Similar findings are reported by Levin, Kirsner and Palmer (49) who studied the nocturnal secretion of duodenal ulcer patients before and after healing. Since hypersecretion continues after healing, it is likely that it existed prior to the ulcer, but there is no evidence available on this point. It might be easily answered, however, in those investigations which involve large groups of normals. In such groups a certain small percentage will be **hypersecretors** with acid responses in the ulcer range. Also, a small percentage of each group may be expected to develop duodenal ulcers. What is the secretory pattern of those who eventually develop ulcer? Do they show normal gastric secretion at present or are they already known to be hypersecretors? If current hypotheses are correct, there may be a high correlation between the present hypersecretion group and those who will develop ulcer disease at a later date.

MECHANISM OF GASTRIC HYPERSECRETION IN ULCER

Why do ulcer patients secrete more HCl than normals do? What is the mechanism by which this hypersecretion is brought about? Is it the result of a pathologic stimulus or simply an exaggeration of physiologic mechanisms? To answer the last question first. The fact that ulcer patients continue to hypersecrete after the ulcer has healed would favor the view that an exaggerated response to physiological stimuli is responsible. Second, it is well known that the secretory patterns of patients with gastric ulcers differ from those with duodenal or gastrojejunal ulcers in that they do not have a hypersecretion of acid in the interdigestive or basal period (76). But if the hypersecretion in ulcer were due to the ulcer (by liberation of histamine from the inflamed tissues or some similar mechanism), then the patients with gastric ulcer should also hypersecrete. Therefore, since their interdigestive secretion is normal or less than normal, it would seem that ulceration per se does not cause hypersecretion.

In regard to the mechanism of hypersecretion, Dragstedt (23) believes that secretory **hypertonus of the vagus nerves** to the stomach is the culprit in most cases of duodenal ulcer. He points out that the excessive

secretion of the interdigestive or basal secretion is reduced to normal or less than normal when vagotomy is performed. Whereas this is certainly strong evidence for the vagal hypertonicity hypothesis, it is not conclusive. There are several other possible explanations which might fit these observations.

The parietal cells may be **abnormally sensitive** to any and all stimuli and may simply be overresponding to vagal (and other) stimuli which are normally present. Dividing the vagus nerves removes tonic or subminimal stimuli, reducing the sensitivity of the parietal cell to a normal level. The observation that ulcer patients hypersecrete to all types of stimuli might be thought to favor the "sensitive cell" hypothesis, as would the fact that the gastric response to all stimuli, including histamine, is decreased by vagus section. The gastric secretory response to all stimuli (except insulin) as well as basal secretion is reduced by the usual partial gastric resection as by vagotomy. In this case the resection may decrease parietal cell sensitivity by removing the influence of the gastrin producing antrum. Of course, partial resection also removes a portion of the parietal cells and thereby effects a commensurate reduction in the quantity of acid produced. If there is hypertonicity of the vagi to the stomach, then one might expect to find evidence of increased tone elsewhere in the parasympathetic system—particularly other branches of the vagi. Little (56) studied fifty ulcer patients and twenty five control patients, observing sixteen physiological variables which are controlled in part by the autonomic nervous system. He failed to uncover any differences in parasympathetic activity between normals and ulcer patients. It is well known, however, that mass discharge is not the rule in the parasympathetic system as it often is in the sympathetic system. Moreover, there is no reason to assume that those vagal fibers which do not go to the stomach (e.g., cardiac) are necessarily involved in hypertonus.

Another possible explanation for the observed hypersecretion might be that all stimuli are normal and the hypersecretion is due simply to a greater than normal **number** of parietal cells. This would assume the tonus of the vagi to be normal rather than increased. Tongen (78) counted the parietal cell density in resected human stomachs and found a fairly high correlation between the concentration (or number) of parietal cells and the preoperative histamine response. He was also able to cause considerable hyperplasia of parietal cells in dogs by chronic histamine stimulation. The pretreatment average count was 96 parietal cells per unit area; after histamine treatment the count was 163 parietal cells. This would seem to be a fertile area for further investigation into the role of the vagus nerves in hypersecretion.

Still another possible explanation might be **hypofunction of the**

**physiologic inhibitory mechanisms** for acid secretion Although the existence of inhibitory influences have been known since Pavlov the physiology of such mechanisms is only now being studied particularly in the laboratories of Dragstedt Woodward Grossman and Harrison What role if any the inhibitory mechanisms may play in the genesis of peptic ulcer remains to be seen

Although the acid hypersecretion of ulcer patients and its reduction by vagotomy have *given rise to many hypotheses none explains it any better* than the vagal hypertonus hypothesis of Dragstedt There are observations which can be explained in several ways but there is very little evidence *against* the vagus hypothesis Moreover there are observations which can be explained *only* by this vagal hypothesis

Acid secretion is controlled by several different mechanisms chemical as well as nervous But pepsin secretion and gastric motility are principally controlled by the vagus If vagal hypertonus is responsible for the acid secretion there should also be an increased pepsin output and increased gastric motility in ulcer patients Most investigators have found that this is the case Ulcer patients have three times as much pepsin in the basal secretion as controls have (44) The motility is increased both as measured radiologically and by balloon technics (72) This would appear to be very strong evidence in favor of Dragstedt s view that the vagus is responsible for the hypersecretion seen in ulcer patients

## EMOTIONS VAGUS NERVES AND PEPTIC ULCER

Most clinicians are agreed that stress particularly mental stress often appears to play a role in the chronic peptic ulcer diathesis The sensitivity of the digestive tract to mental disturbances was early recognized and finds frequent expression such as the following observation from Blumenbach in 1817

> The stomach is amply furnished with nerves from each nervous system whence arises its great sensibility from which it is so readily affected by all kinds of nerve stimuli whether external as cold or internal as food and its own fluids or mental whence also the great and surprising sympathy between it and most functions of the system to which are referrible [sic] the influences of all passions upon the stomach and of the healthy condition of the stomach upon the tranquillity of the mind (8)

The possible mechanisms by which mental stress initiates or perpetuates an ulcer remain somewhat obscure in spite of the great amount of thought and research devoted to the etiology of ulcer Widely quoted in discussions of the neurogenic aspects of peptic ulcer is Cushing s *Peptic Ulcer and the Interbrain* (19) in which he concludes

So it may easily be that highly strung persons who incline to the form of nervous instability classified as parasympathetic (vagotonic) through emotions or repressed emotion incidental to continued worry and anxiety and heavy responsibility combined with other factors such as irregular meals and excessive use of tobacco are particularly prone to have chronic digestive disturbances with hyperacidity often leading to ulcer

Cushing presented nine cases of acute ulcers erosions or widespread malacia of the esophagus stomach or duodenum plus one subacute and one chronic duodenal ulcer all of which followed surgery of the central nervous system The number of chronic duodenal ulcers found by Cushing was remarkable remarkable in that he found so few in his tremendous experience with intracranial tumors In the light of current knowledge it would appear that Cushing fostered at least two misconceptions first that postoperative acute ulcers are particularly prone to follow intracranial operations and second that such acute often agonal ulcers are "wholly comparable to chronic peptic ulcers These criticisms however in no way detract from the great contribution that this paper made in orientation and clarification of thought regarding the etiology of peptic ulcer

Cushing's report of acute upper gastrointestinal ulcerations following intracranial operations has since been confirmed by many but it is also true that acute ulcers occur after major surgery in other regions of the body Thus McDonnell and McCloskey (59) found a 3 24 per cent incidence of acute ulcers in autopsy material following surgery on other than the central nervous system and a 2 78 per cent incidence following central nervous system lesions Fletcher and Harkins (34) reported forty two autopsy cases of acute ulcer that followed surgery burns trauma and a variety of serious medical diseases They felt that their data supported the view that there is a correlation between the severity of the original disease and the likelihood of secondary acute ulcer formation There is considerable recent work which cannot be detailed here that implicates the hypothalamus hypophysis adrenal axis in these acute stress ulcers

Gray and colleagues (37) and Porter Movius and French (66) have presented evidence which in Gray's words "suggests that chronic emotional and physical stress is transmitted to the stomach by a hormonal mechanism mediated through the adrenal gland and may induce gastrointestinal ulceration through the hypothalamic pituitary gastric pathway Most workers have been unable to obtain evidence that would indict the adrenal mechanisms in chronic peptic ulcer One source of conflict may be the disagreement about uropepsin as a mirror of gastric secretory activity Bigler *et al* (68) concluded that uropepsin levels are independent of gastric secretion activity [but that] uropepsin may be a sensitive and accurate index of adrenal activity" Hirschowitz and Streeter (40) have evi

dence that the observed increase in urinary pepsinogen excretion following ACTH results from an increased clearance of pepsinogen by the kidneys This is not to deny however that the adrenal mechanism may often be implicated in upper gastrointestinal ulceration It appears to play a major role in acute stress ulcers and it is well known that ACTH or cortisone therapy may activate a quiescent peptic ulcer But most evidence indicates that the ulcerogenic action of these drugs cannot be accounted for by a steroid induced hypersecretion alone the gastric secretions may be increased decreased or unchanged Lillehei Roth and Wangensteen (53) showed that "a number of stress provoking agencies in experimental animals fail to influence gastric secretion or even depress gastric acidity but nevertheless they exert a powerful ulcer abetting effect by reducing the resistance of the gastroduodenal mucosa to autodigestion It may be that the mucosal resistance is lowered by local vascular changes and by an attenuated mucus barrier

## EFFECT OF EMOTIONS ON GASTRIC SECRETION AND MOTILITY

Cannon (12) held that stressful situations produce a decreased gastric secretion and motility This is a part of the flight or fight defense reaction in which there is a general decrease in digestive and reproductive functions and a general increase in sympathetic functions such as heart rate blood pressure and glycogenolysis Teleologically this appears logical—but illogical perversions of physiological mechanisms may occur

Wolf and Wolff (80) have found that the human stomach reacts to fear dejection guilt hopelessness or despair by a decreased secretion and motility But anxiety anger and resentment and frustration provoke a diametrically opposite response an increased gastric secretion and motility Their most extensive observations were made on Tom a man with a surgically created gastric fistula following a benign stricture of the esophagus They later studied three other men with gastric fistulae One of these is of particular interest to this discussion because observations were made before and after bilateral vagus section Before his vagotomy in discussing a physician who the patient thought had treated him badly the subject became angry and hostile whereupon hypersecretion and hypermotility occurred After vagus section although the patient became just as emotional when asked about the quack there was no change in gastric secretion or motility

Todd (77) made extensive radiographic observations on the effects of various emotions on the gastric motility He found that fear disappointment or the strain of mental depression was accompanied by a decrease

in gastric tonus and weak or absent peristalsis But in the "anxiety complex" the stomach always manifested hyperactivity

Mahl (57) measured the basal or interdigestive phase of gastric acidity in eight university students during a relatively quiet period in the school year the measurements were repeated just before an important final examination There was a significantly higher acidity in six of the eight students which he attributed to their anxiety

A lawyer who had been hospitalized for treatment of a duodenal ulcer and who fancied himself as quite a chess player was challenged to a game by Dr James S Clarke (63) After the Levin tube was placed into the fasting patient's stomach and connected to the Wangensteen suction apparatus Clarke proceeded to frustrate the patient in a game of chess the patient was beaten rather badly As the tension mounted in the game so too did the gastric secretion mount as measured by the rate of accumulation of gastric contents in the collecting bottle His resentment and hypersecretion apparently lasted for some hours since the night secretion which had been 71 mEq HCl the night before rose to 134 mEq the night of the chess game secretion fell to 81 mEq the following night

A similar observation was made by Szasz *et al* (74) on another patient prior to and after vagotomy This was a 23 year old male laborer with a five year duodenal ulcer history

The patient had been on continuous gastric suction with a Wangensteen apparatus for 41 hours previously In connection with other studies the administration of enterogastrone was started at 9 00 A M of this day gastric contents were collected and measured every hour on the half hour A complete inhibition of gastric acidity was induced by enterogastrone

The psychiatric interview began at 1 30 P M Approximately one hour later as the topic of conversation shifted to increasingly more personal matters the patient became somewhat anxious and soon quite hostile to the interviewer It was noted that whereas at the very beginning of the interview there was only a slow stream of gastric secretion being aspirated through the tubing of the Wangensteen apparatus gastric juice was now pouring forth profusely Of particular interest was a complete inhibition of free hydrochloric acid in the secretion induced by the injection of enterogastrone before the psychiatric interview When the patient experienced intense anger which he could not express adequately in words there was an outpouring of free hydrochloric acid the inhibition of enterogastrone was thus apparently overcome Moreover the secretion of gastric juice per unit of time both as to volume and free acidity was greater during this period of psychologic stimulation than at any other time during the period of observation

The attempt at psychologic stimulation of gastric secretion was repeated ten days after the patient underwent a bilateral subdiaphragmatic vagotomy and a gastroenterostomy The procedure was identical to that applied before the oper

dence that the observed increase in urinary pepsinogen excretion following ACTH results from an increased clearance of pepsinogen by the kidneys This is not to deny however that the adrenal mechanism may often be implicated in upper gastrointestinal ulceration It appears to play a major role in acute stress ulcers and it is well known that ACTH or cortisone therapy may activate a quiescent peptic ulcer But most evidence indicates that the ulcerogenic action of these drugs cannot be accounted for by a steroid induced hypersecretion alone the gastric secretions may be increased decreased or unchanged Lillehei Roth and Wangensteen (53) showed that "a number of stress provoking agencies in experimental animals fail to influence gastric secretion or even depress gastric acidity but nevertheless they exert a powerful ulcer abetting effect by reducing the resistance of the gastroduodenal mucosa to autodigestion" It may be that the mucosal resistance is lowered by local vascular changes and by an attenuated mucus barrier

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mediated principally through the vagus nerves since motor function as well as secretory function is affected and since the response is abolished by vagotomy

*It is very tempting to ascribe a major role to anxiety hostility and* similar emotional stresses in the initiation and perpetuation of peptic ulcers A great deal more objective evidence must be obtained before the contribution of the emotions can be quantitatively evaluated however If one digs hard enough in the clinical history of any patient some sort of emotional problem can be found and some *post hoc ergo propter hoc* reasoning is somewhat dangerously engaged in It should be borne in mind that a patient with burning epigastric pain may well be rather anxious about his pains Cancer is one of the possibilities which crosses his mind Then too there is the collective conceit of our contemporary civilization which fosters the belief that our harried existence is much tougher upon the psyche than that of past generations But one wonders if the threatened loss of an account by a Madison Avenue businessman is any more traumatic than the anxiety about where the next meal is coming from a daily problem to which the happy carefree native was often exposed For example Schweitzer (70) tells of certain tribes in the upper Ogowe region in Africa which often sell their children into slavery in order to save them from starvation Yet the incidence of peptic ulcer in the African native is said to be low This suggests that an awareness of threatening concern about an event may be as important as the act itself

Several facts emerge from the foregoing considerations most ulcer patients (and some normals) hypersecrete emotional stress (cephalic phase) increases gastric secretion and the stress phenomenon mediated through the adrenals may reduce local mucosal resistance Many ulcer patients correlate onset and exacerbation of ulcer symptoms with periods of stress Consider for example a person with a stomach that hypersecretes and is hypermotile because of constitutional vagal hyperactivity Expose this person to a period of stress with its associated disturbed sleeping and eating habits too much smoking coffee and alcohol If protracted the mental stress further increases the gastric secretion via the gastric components of the vagus nerves and the stress response of the adrenals and its possible decrease in mucosal resistance may result in acute peptic ulcer of the duodenum This ulcer may then become chronic if the stress continues or if the constitutional vagal hyperactivity is sufficient to be a factor in chronicity

The relative importance of the constitutional vagal hyperactivity and ulcer susceptibility may vary from person to person For example a person with very active vagi would require only a minor emotional upset to develop an ulcer Such a person would likely be a chronic problem since

ation except that no enterogastrone was given The psychologic stimulus of anger now did not result in any significant increase in either the volume or free acidity (concentration as well as quantity) of the gastric secretion [see Fig 8]

Still another observation of the effect of anxiety on the gastric secretion was made by Dragstedt *et al* (32) who presented data on the fasting secretion (twelve hour basal or interdigestive) in eighty five duodenal

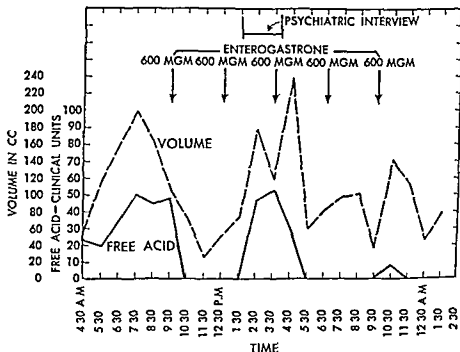



Fig 8 —Stimulation of hydrochloric acid secretion by intense feeling of anger (hostility) during administration of enterogastrone (Courtesy Szasz Levin Kirsner and Palmer 74 )

ulcer patients The overnight secretions were measured during the third night before surgery the second night and finally during the night preceding surgery On the average these patients secreted 48 5 mEq on the third night 18 mEq on the second night and 67 5 mEq on the night before surgery The authors comment "It is interesting to speculate that this may be related to possible apprehension or anxiety concerning the forthcoming operation

The evidence presented above would indicate that the human stomach may respond to some forms of emotional stress by an increase in secretory and motor activity Further this gastric response to psychological stress is

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the hyperactive vagi constitute a potent chronicity factor. On the other hand, a person with relatively normally active vagi could tolerate a considerable amount of stress before developing an ulcer, and his ulcer would probably heal if the stress factors were relieved.

As information is gained concerning the etiology and pathogenesis of benign peptic ulcer of the duodenum or gastrojejunal stoma, it becomes progressively more clear that division of the vagus nerves to the stomach is the rational method of surgical therapy. This operation is not aimed at the *manifestations of the physiological abnormalities,* such as the hypersecreting stomach. Vagotomy gets at the primary problem—the overactive cephalic phase and its untoward effects upon hypersecretion mediated via the vagus nerves to the stomach. By dividing the vagi, the constitutional hyperactivity of the nerves is abolished. But, just as important, the hypersecretion caused by emotional stress is also abolished, since the connections between the troubled brain and the stomach are divided.

It is the reasonable and proper desire for physicians to prevent disease whenever possible, thereby avoiding the necessity for treatment. The following advice was offered by Leroy (Satchel) Paige (64), the ageless baseball pitcher, on how to stay young. It can probably be applied equally well when the desire is to avoid the development of an ulcer.

1. Avoid fried meats which angry up the blood.
2. *If your stomach disputes you, lie down and pacify it with cool thoughts.*
3. Keep the juices flowing by jangling around gently as you move.
4. Go very light on the vices, such as carrying on in society. The social ramble ain't restful.
5. Avoid running at all times.
6. Don't look back. Something might be gaining on you.

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EDWARD R WOODWARD

# 3 *Physiology of the Gastric or Antral Phase of Secretion*

The **gastric phase** of gastric secretion is related primarily to the hormonal influence exerted by the **gastric antrum** It is therefore also known as the **antral phase** of gastric secretion

The use of the antrum exclusion operation to avoid the difficult and dangerous dissection involved in posterior penetrating duodenal ulcer was first described by von Eiselsberg (8) It became popular because of this safety feature and was used in a great number of patients treated by Finsterer (10) who called it "resection for exclusion" The procedure was also advocated by Devine (2) who referred to it as his "alkalizing operation" In fact the operation for antral exclusion gained considerable popularity in surgical circles everywhere During the years 1938-45 however there were disquieting reports from Ogilvie (28) Wangensteen (42) and Allen and Welch (1) indicating a high incidence of gastrojejunal marginal ulceration in patients previously subjected to the antral exclusion operation The following case report illustrates this problem as well as pointing to others

M S a 36 year old white married meat salesman first came to the University of Chicago Clinics in 1938 At this time the patient complained of periodic bouts of epigastric pain which developed one to two hours after meals his pain was relieved only by food or antacids X ray examination revealed duodenal ulcer with crater He received treatment on an outpatient basis until October of 1940 when a bout of acute obstruction precipitated his first hospital admission He responded well to medical therapy but required a month of hospital care Roent

genograms revealed persisting high grade pyloric stenosis In 1942 obstructive symptoms recurred Two hospitalizations failed to achieve lasting relief and in February 1943 the patient was admitted to the surgical service in a state of severe alkalosis serum chloride was 80 2 mEq/l Following the requisite electrolyte repletion operation was performed on March 1 1943

A large inflammatory mass about the proximal duodenum was found with the pancreas densely adherent to the duodenum on its superior and posterior aspects Therefore it was decided to perform a Finsterer exclusion gastrectomy The stomach was transected about two inches proximal to the pylorus and the distal end was closed A three quarter gastric resection was then performed with a retrocolic Polya anastomosis The patient recovered rapidly and was discharged on the thirteenth postoperative day

He remained well for only five months In August of 1943 he noted a recurrence of lower abdominal and lumbar pain particularly severe at night which was relieved by food fluids or belching X ray films revealed a huge crater in the jejunum immediately opposite the anastomosis (Fig 1) The patient was treated with X ray therapy directed to the body and the fundus of the stomach Histamine achlorhydria ensued with remission of the gastrojejunal ulcer But one year later the ulcer distress recurred and X ray films again disclosed a large marginal ulcer In addition there was a prompt reflux of barium through the afferent jejunal loop into the duodenum through the pylorus and into the excluded antrum (Fig 2)

The case reported above particularly the X ray findings portrayed in Figure 2 and these reports from the literature raised the question whether the excluded antral part of the stomach might in some way stimulate the secretion of acid gastric juice Certainly if barium could reflux the full length of the afferent loop into the isolated antral segment food substances could also be expected not only to come in contact with antral mucosa but also to distend the antral lumen thereby stimulating its function

The possibility that the antrum of the stomach might elaborate a hormone which mediated the gastric or antral phase of gastric secretion was first postulated by Edkins in 1906 (6) Influenced no doubt by the demonstration by Bayliss and Starling only four years earlier of the pancreatic secretin mechanism Edkins was struck by the distinctive histological structure of the pyloric antrum especially its complete lack of parietal and chief cells He reported studies wherein the intravenous administration of extracts of antral mucosa stimulated gastric secretion extracts similarly prepared from other parts of the stomach were without effect Further studies were carried out on animals in which the antrum was separated from the body of the stomach by a mucosal diaphragm (7) The introduction of food substances into the antrum was followed promptly by the secretion of acid gastric juice in the body of the stomach These

results were considered to indicate the presence of a hormonal mechanism Edkins coined the name gastrin for the antral hormone

During the four decades that followed Edkins original observations the status of his gastrin hypothesis was a controversial one Ivy and Whitlow (17) in repeating the experiments of Edkins and Tweedy found no significant increase in secretion of the fundus when foodstuffs were introduced into the antrum They pointed out that the secretion secured by the earlier workers was so meager in amount as to fall within the range of the basal secretion and was thus without significance They put the gastrin theory to physiological test by preparing animals with a Pavlov pouch and an isolated pouch of the antrum Even prolonged contact of the antral mucosa with many foodstuffs failed to stimulate gastric secretion from the Pavlov pouch In a similar experiment Priestley and Mann (31) like



FIG 1 —X ray film showing huge marginal ulcer opposite gastrojejunal stoma five months after Finsterer exclusion gastrectomy

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wise reported no secretion of gastric juice as a result of stimulation of an isolated antral pouch in dogs with a fundic fistula

Studies on the effect of excision of the antrum in experimental animals gave conflicting results Portis and Portis (30) Shapiro and Berg (35) and Thompson (39) found no change in the secretion from isolated stomach pouches following resection of the gastric antrum However Smidt (36) reported marked reduction in the secretion of gastric juice from a Pavlov pouch after removal of the antrum Likewise Wilhelmj and colleagues (43 44 45) found a reduction of acidity in the gastric juice of dogs after resection of the antrum

Further studies with pyloric extracts have also been confusing As Ivy and Whitlow (17) point out "It is not correct to assume that pharmacological action denotes physiological significance" The studies of Keeton Koch and Luckhardt (21) demonstrated the non specificity of the gastric secretagogue for the antrum they were able to obtain the same effect with extracts from many other tissues including some outside of the gastro intestinal system It became apparent that the active principle in all of these extracts was histamine In other studies however histamine free extracts of the antrum with definite gastric secretory activity have been prepared by the same experimenters and by Komarov (22) More recently Jorpes (19) has extended Komarov s extraction technic to obtain a highly refined and potent gastrin which he believes to be a protein containing substance

The experience of surgeons with the antrum exclusion operation seemed to refute the predominantly negative physiologic studies which followed the initial report of Edkins and on this basis it was felt that reinvestigation of the problem was warranted Using the collection technic devised by Dragstedt Haymond and Ellis (3) it was possible to assemble reliable quantitative data A defect common to many previous reports was reliance upon qualitative measurements of the concentration of free acid in samples collected There is now general agreement that the secretion of parietal cells is manufactured at a constant acidity and that variations in the acidity of the gastric content are due to the presence of neutralizing substances In gastric pouch preparations very little neutralizing material is present so that the volume of secretion may be greatly reduced without a corresponding reduction in the concentration of free acid With these thoughts in mind we embarked upon a series of experiments in the fall of 1946 some of these are described below

## EFFECT OF ANTRUM ABLATION ON GASTRIC SECRETION

Isolated small stomach pouches of the Pavlov or Heidenhain variety were prepared in a series of mongrel dogs (see p 79) Following recovery by



Fig 2.—X ray film showing reflux of barium into excluded antrum

the acidity fell from about 120 mEq/l to about 95 mEq/l It was also noted that incomplete resection of the antrum was followed by persistence of relatively large volumes of pouch secretion even though the retained antral remnant was rather small

These studies showed that **resection of the gastric antrum produced an extensive reduction in the secretion of acid gastric juice** in dogs prepared with Pavlov or Heidenhain pouches It was apparent that the major stimulus responsible for the secretion of acid gastric juice by these isolated pouches was in some way related to the presence of the antrum Encouraged by these promising results the problem was re-examined and approached in another way

## EFFECTS OF ANTRUM TRANSPLANTATION ON GASTRIC SECRETION

In the first of our antrum transplant experiments our objectives were to remove the antrum from gastrointestinal continuity and to reintroduce it by stages into the second part of the duodenum Thereby complete denervation of both the parasympathetic and sympathetic nerve supply of the antrum was achieved The animal preparation used included a totally isolated stomach pouch with the vagi cut the pouch originally described by Lim Ivy and McCarthy in their classic demonstration of the intestinal phase of gastric secretion (24)

As in the previous experiment the dog was maintained on a carefully weighed diet quantitative daily collections of gastric secretion were made After a long observation period reoperation was performed The dividing point between the antrum and body of the isolated stomach was determined and the anterior wall divided On the posterior wall and lesser curvature only the mucous membrane was divided The antral segment was then sutured to a window created in the duodenal wall Preservation of the posterior seromuscular connection between antrum and body of the stomach as well as the lesser curvature structures maintained an adequate blood supply to the antral transplant After recovery from this procedure quantitative collections of gastric secretion were again made over long periods of time Careful attention was given to the maintenance of electrolyte balance

After a period of eight to twelve weeks we performed the last of the staged operative procedures The posterior seromuscular layer and the structures of the lesser curvature were completely transected leaving the antral transplant completely devoid of its original blood and nerve supply The anastomotic line previously created between antrum and duodenum allowed enough blood supply to maintain viability of the transplant

The results (5) of the experiment are presented in Figure 4 During

the dogs after surgery continuous daily collections were made of the gastric juice secreted by the isolated pouches using a detachable rubber bladder secured to the cannula by a threaded nipple The animals were maintained on a carefully weighed standard diet reinforced with electrolytes in quantities adequate to replace those lost from the pouch After long periods of observation had revealed a constant level of secretion the animals were reoperated upon and resection of the antrum performed Following recovery from the second operative procedure collections of pouch secretion were resumed on the same dietary program

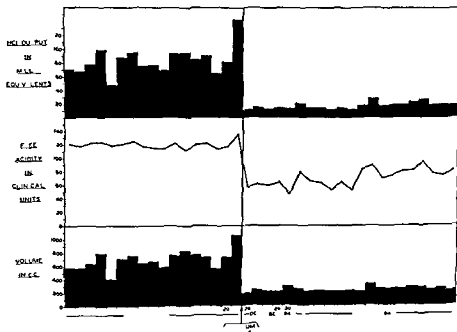



FIG 3 —The effect of antrum resection in Pavlov pouch dog (daily 24 hour secretion)

The results were both constant and dramatic Findings in the first four animals were reported in 1948 (46) These disclosed that the average twenty four hour production of hydrochloric acid output was reduced 64–95 per cent the average reduction was 84 per cent A more extensive report was later made of the results obtained in eleven dogs with Pavlov or Heidenhain pouches in which antrum resection had been performed (47) It was frequently noted that the major diminution in secretion was a fall in volume (Fig 3) Antrum resection in a dog with a Pavlov pouch was followed by a striking reduction in the hydrochloric acid output However the fall in the concentration of free acid was less than might be expected from the extensive reduction in the volume of the gastric juice

These data strongly suggest that after complete interruption of the extrinsic nerve supply to the antrum followed by the complete separation of vascular and neuromuscular connections to the remainder of the stomach the antrum when exposed to the contents of the duodenum powerfully stimulates the body of the stomach to secrete acid gastric juice These facts fulfil the requirements defining a hormonal mechanism confirm Edkins original hypothesis and demonstrate that **the antrum of the stomach functions as an endocrine organ**

The next transplantation experiment was designed to test the specificity of the antrum in the gastric phase of gastric secretion The test prepara-

TABLE 1

EFFECT OF TRANSPLANTATION OF ANTRUM INTO DUODENUM IN TOTAL POUCH DOGS
(24 Hour Secretions)

| Dog No. | Vagus Innervation of Antrum | Secretion in Preliminary Control Period | | | Secretion after Antrum Transplantation | | |
|---|---|---|---|---|---|---|---|
| | | Volume (Cc) | Free Acid (C U) | HCl Output (mEq) | Volume (Cc) | Free Acid (C U) | HCl Output (mEq) |
| D 52 | Severed | 70 | 33 | 2 | 622 | 123 | 77 |
| D 136 | Severed | 130 | 41 | 5 | 436 | 114 | 51 |
| D 181 | Severed | 173 | 42 | 7 | 890 | 136 | 119 |
| D 182 | Severed | 126 | 72 | 9 | 575 | 130 | 75 |
| D 173 | Intact | 300 | 105 | 32 | 1 056 | 145 | 153 |
| D 178 | Intact | 514 | 120 | 62 | 1 575 | 144 | 227 |
| D 183 | Intact | 565 | 112 | 63 | 1 561 | 139 | 217 |
| D 185 | Intact | 290 | 99 | 29 | 1 264 | 125 | 158 |

tion was a totally isolated stomach pouch with the vagi cut Instead of transplanting the antrum into the duodenum a comparable amount of the body of the stomach was transplanted An elliptical area on the greater curvature was selected since the short gastric vessels from the splenic pedicle would insure an adequate blood supply After the preliminary control period this transplant was performed creating a window of comparable size in the duodenal wall to complete the diverticulum The results are shown in Figure 5 The low level of gastric secretion obtained during the control period persisted completely unchanged throughout the period of transplant The experiment was repeated in two other animals in none of the three was there a significant change in gastric secretion following the transplant It was concluded that **the hormone mediating the gastric phase of gastric secretion is elaborated only by the antrum** and is specific for this structure

The next series of transplantation experiments was designed to ascer-

the initial control period the levels of acid secretion obtained were very low This was expected since the vagi were cut and the antrum removed from contact with ingested food substances At this point of the study therefore only the intestinal phase of gastric secretion was operative With creation of a stoma between antrum and duodenum as noted in the second drawing of Figure 4 the duodenal contents gained access to the antrum and its mucosa The daily gastric secretion increased from less than 5 mEq to nearly 100 mEq in response to feeding

At the next stage *with complete denervation of the antrum* high levels

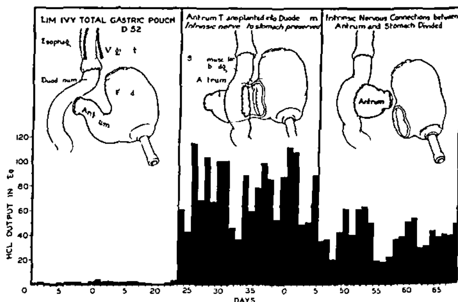



FIG 4 — The effect of antrum transplantation and denervation on gastric secretion

of gastric secretion were maintained although on the average somewhat less than during the first phase of the transplantation It was thought that this might reflect the rather drastic reduction in available blood supply to the antrum The experiment was repeated in two other dogs and whereas the pronounced augmentation of secretion at the second stage occurred in both the decrease after denervation was not present The staged transplantation of the antrum into the duodenum was performed in a total of eight dogs four with the vagi cut and four with the vagi preserved The results are presented in Table 1 The enormous levels of secretion obtained in the animals with functional vagal innervation to the stomach are noted after antrum transplant two animals averaged over 1 500 cc per day of highly acid gastric juice

The findings were interpreted as demonstrating **the necessity for contact between gastrointestinal contents and antral mucosa for the formation of gastrin** at least under the conditions of this experiment The very striking hypersecretion of gastric juice by the Heidenhain pouch which followed transplantation of the antrum into the transverse colon is a much more complex phenomenon related to the pH of the environment in which the antrum is located This marked hypersecretion has been utilized as another method for producing experimental peptic ulcer (see chap 4)

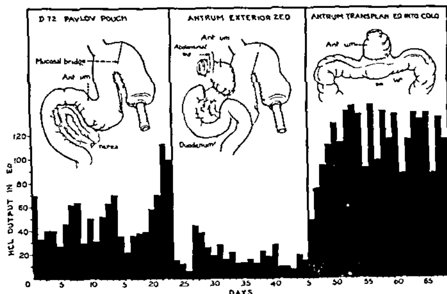



Fig 6 —Hypersecretion from Pavlov pouch after antrum transplantation into colon

## THE THEORY OF ACID INHIBITION OF ANTRUM FUNCTION

Sokolov working in Pavlov s laboratory discovered that the introduction of 0 5 per cent HCl into the stomach or of gastric juice into the duodenum markedly diminished the secretion from a Pavlov pouch (37) In subsequent studies of this phenomenon attention has been focused on the inhibition of gastric secretion by the presence of acid in the duodenum Pincus Thomas and Rehfuss (29) showed that introduction of HCl into the duodenum did not depress gastric secretion unless the duodenal pH fell to approximately 2 5 However Wilhelmj *et al* (43) demonstrated clearly that acid can inhibit the gastric phase of secretion

In the Heidenhain or Pavlov pouch dog transplantation of the antrum into the colon obviously removes the antrum from its normal proximity to

tain the function of the antrum when it was moved into various locations Three dogs were prepared with Pavlov pouches After the initial control period on a carefully regulated dietary and electrolyte intake the antrum was removed from gastrointestinal continuity the proximal end was closed and the pyloric end brought through a stab wound as a cutaneous fistula After repetition of the secretory study the antrum was relocated from its position in the abdominal wall to the transverse colon where it was sutured as a diverticulum The vascular pedicles on both the lesser and the greater curvatures were found to be easily preserved, so that viability of the transplant was not a problem Again the quantitative collections of gastric juice were made from the cannula in the Pavlov pouch

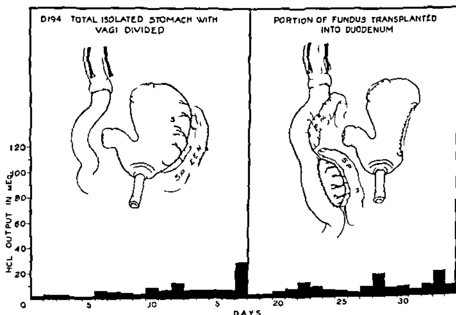



Fig 5 —The negative effect of transplanting the body of the stomach into the duodenum

The secretory results of this procedure are presented graphically in Figure 6 During the control period this animal secreted an average of 51 mEq of HCl per twenty four hour period When the antrum was exteriorized this average fell to 18 mEq per day [1] When the antrum was introduced into the colon as a diverticulum a tremendous augmentation of pouch secretion occurred this averaged 115 mEq per day or over twice the secretion obtained with the antrum in its normal location Comparable results were obtained in the other two animals

[1] It is to be noted that vagi on the lesser curvature were cut at the time of this transplantation further work (11 26) has shown the importance of vagal innervation to gastrin release from the exteriorized antrum

The findings were interpreted as demonstrating the necessity for contact between gastrointestinal contents and antral mucosa for the formation of gastrin, at least under the conditions of this experiment. The very striking hypersecretion of gastric juice by the Heidenhain pouch which followed transplantation of the antrum into the transverse colon is a much more complex phenomenon related to the pH of the environment in which the antrum is located. This marked hypersecretion has been utilized as another method for producing experimental peptic ulcer (see chap. 4).

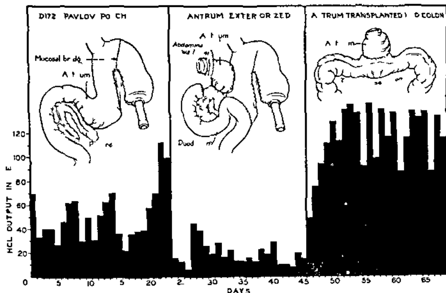



FIG. 6.—Hypersecretion from Pavlov pouch after antrum transplantation into colon

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In the Heidenhain or Pavlov pouch dog transplantation of the antrum into the colon obviously removes the antrum from its normal proximity to

the acid secreting part of the stomach To test the hypothesis that acid has an important regulatory role in the hormonal function of the antrum a series of experiments was designed which altered the acidity of its environment

THE ACID CUFF ANTRAL TRANSPLANT

Of all fundic pouch preparations the *Heidenhain pouch is probably the* most useful as a bio assay method for measuring gastrin production by the antrum Since the pouch has no vagal innervation this variable is eliminated and perhaps related to this factor the basal secretory activity of the pouch is very nearly nil Maintenance of a state of adequate nutrition plus fluid and electrolyte balance in an animal with a partial stomach pouch is relatively easy Therefore in this experiment four dogs were prepared with Heidenhain pouches The antrum was then transplanted in each case into the transverse colon along with a generous "cuff of the immediately proximal acid secreting portion of the stomach The cuff was left at the apex of the diverticulum and the pyloric end of the transplant was anastomosed to the colon After recovery and an observation period quantitative collections of pouch secretion were made Another laparotomy was then performed and the acid secreting cuff was excised from the apex of the antral transplant Again the animal was placed on the standard dietary program and quantitative collections of gastric juice were repeated

In all four dogs there was a distinct increase in pouch secretion following excision of the antral cuff although in one animal this was not striking (27) The data from one such study along with a diagram of the experiment are presented in Figure 7 These data support the hypothesis that the presence of **acid secreting tissue,** in some way **inhibits the hormonal mechanism of the antrum**

VAGOTOMY OF THE MAIN STOMACH IN HEIDENHAIN POUCH DOGS

Since vagotomy abolishes the nervous phase of gastric secretion the resultant decrease in gastric acidity might produce an alteration in the gastric phase of gastric secretion Experiments from two laboratories (9 14) have shown that transthoracic vagotomy *increases* the secretion of gastric juice from a Heidenhain pouch

The paradox that gastric secretion in the main stomach is decreased by vagotomy but secretion of acid gastric juice by the Heidenhain pouch is increased is a striking example of the interaction of physiological mechanisms Abolishing the cephalic phase exerts a pronounced stimulatory effect via the gastric phase as established by absence of this phenomenon following resection of the antrum Vagotomy not only decreases acid se

cretion in the main stomach but it also has a potent effect on gastric motility with marked delay in gastric emptying The resultant retention keeps food substances in prolonged contact with the antrum the distention of the stomach may also act as a mechanical stimulant for gastrin production That the motility factor may be even more important than the reduction in acidity is apparent from experiments where gastroenterostomy prevented the stimulatory effect of vagotomy in the Heidenhain pouch preparation

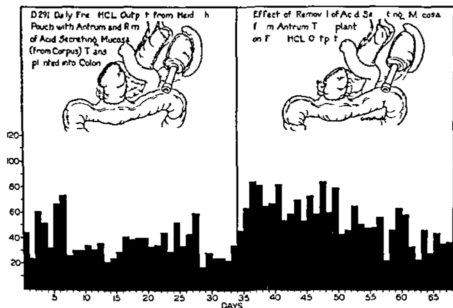



FIG 7 —Influence of an acid secreting cuff on an antrum transplant in the colon

GASTROENTEROSTOMY IN THE HEIDENHAIN POUCH DOG

The construction of a gastrojejunal anastomosis allows reflux of alkaline duodenal juices into the stomach this might be expected to alter the pH of the antrum toward neutrality Experiments have disclosed that gastro enterostomy is frequently followed by an increase in Heidenhain pouch secretion which indicates increased gastrin production (48 54) If the anastomosis is small and placed near the pylorus no stimulatory effect is noted in most cases Similar findings have been reported by Harkins and co workers who have also found that pyloroplasty does not alter the gastrin mechanism (15 19 25) This latter finding is an important factor in the preferential use of pyloroplasty instead of gastroenterostomy in conjunction with vagotomy in the treatment of duodenal ulcer disease

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cretion in the main stomach but it also has a potent effect on gastric motility with marked delay in gastric emptying The resultant retention keeps food substances in prolonged contact with the antrum the distention of the stomach may also act as a mechanical stimulant for gastrin production That the motility factor may be even more important than the reduction in acidity is apparent from experiments where gastroenterostomy prevented the stimulatory effect of vagotomy in the Heidenhain pouch preparation

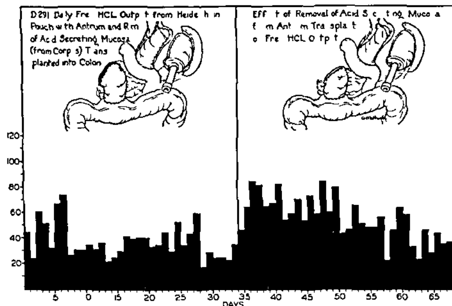



Fig 7 —Influence of an acid secreting cuff on an antrum transplant in the colon

GASTROENTEROSTOMY IN THE HEIDENHAIN POUCH DOG

The construction of a gastrojejunal anastomosis allows reflux of alkaline duodenal juices into the stomach this might be expected to alter the pH of the antrum toward neutrality Experiments have disclosed that gastroenterostomy is frequently followed by an increase in Heidenhain pouch secretion which indicates increased gastrin production (48 54) If the anastomosis is small and placed near the pylorus no stimulatory effect is noted in most cases Similar findings have been reported by Harkins and co workers who have also found that pyloroplasty does not alter the gastrin mechanism (15 19 25) This latter finding is an important factor in the preferential use of pyloroplasty instead of gastroenterostomy in conjunction with vagotomy in the treatment of duodenal ulcer disease

Although definite clinical lessons and potential hazards are apparent from the data presented one can only surmise that the effects noted were due to the presence of alkaline material in the region of the antrum For these reasons experiments were designed toward more accurate control of antral pH

## USE OF THE ISOLATED GASTRIC ANTRUM TO STUDY ACID INHIBITION

Ivy and Whitlow (17) and Priestley and Mann (31) used dogs prepared with isolated pouches of the gastric antrum in an attempt to confirm Edkins gastrin hypothesis Despite their negative results it was felt that direct control of the antral environment was the essential next step in establishing the significance of pH in the gastrin mechanism Many of the substances tested by these workers were acid in reaction and this factor may have accounted in part for the negative results They also severed *the vagal innervation we felt* that preservation *of the* vagi *might render* the antrum more susceptible to stimuli

A surgical technic was devised for isolating the gastric antrum using the method of Pavlov in constructing a double layered mucosal barrier (Fig 8) In this way the vessels and nerves of the lesser curvature were preserved intact A short incision was made on the greater curvature of the stomach at the junction of the antrum and body A marker was placed on the lesser curvature to indicate the limit of the antrum The mucosa was then undermined across the anterior and posterior walls of the stomach this undermining was connected across the lesser curvature The undermined mucous membrane was divided using an infolding suture the mucous membrane of the antrum was closed distally and the mucous membrane of the body was closed proximally thus creating the double layered barrier The pylorus was divided and the proximal end brought to the skin as a cutaneous fistula providing access to the isolated antrum Gastrointestinal continuity was restored usually by means of a Shoemaker Billroth I end to end gastroduodenostomy Part or all of the body of the stomach was used as an indicator of gastrin release through the use of a gastric fistula isolation of the entire stomach or construction of a Heidenhain pouch Subsequent experience has established the last as the most satisfactory indicator mechanism

Two mistakes were made in the technic as originally used First a cannula was placed in the antrum so that through and through perfusion could be performed Many of these dogs had an extremely high rate of basal gastric secretion and subsequent studies by Rigler and Dragstedt (32) disclosed that this disappeared with removal of the antral cannula In the light of present knowledge it is realized that the cannula acted as

a mechanical stimulus for gastrin release Second many dogs with an isolated innervated antrum have a high level of basal secretion even in the absence of a cannula as demonstrated particularly by Forrest (11) and Oberhelman *et al* (26) This can be overcome by including some acid secreting mucous membrane in the isolated antrum an innovation which has the added advantage of making the antral pouch larger so that experiments with perfusion or distention are technically easier

CHEMICAL STIMULATION OF THE ISOLATED ANTRUM

Our method for studying chemical stimulation of the gastrin mechanism is as follows The dog is fasted overnight and placed in the Pavlov stand

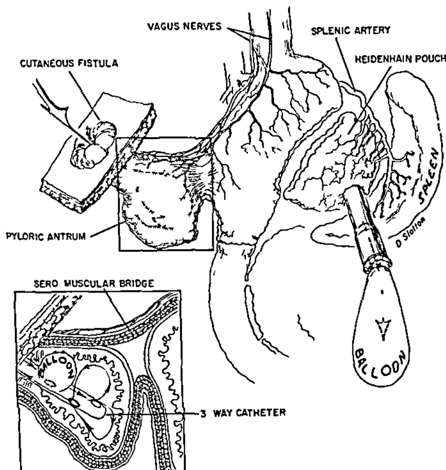



FIG 8 —Isolated gastric antrum with preservation of blood and nerve supply Heidenhain pouch as indicator of gastrin release

Collections are made from the Heidenhain pouch until it is apparent that the basal secretory rate is low and no free acid is present A small (No 10 French) rubber catheter is introduced into the antrum through the pyloric fistula and is held in place by a cord looped over the animal's back Perfusions are made at a constant temperature (21°–23° C ) and constant pressure (40 in between flask and antral pouch) A standard volume usually 250 cc of the solution to be tested is perfused through the antrum over a standard length of time usually one hour In each case the test perfusion is controlled with a similar quantity of physiological salt solution

TABLE 2

EFFECT ON GASTRIC SECRETION OF LIVER EXTRACT IN ISOLATED ANTRUM

| TIME SINCE START OF PERFUSION (HOURS ELAPSED) | COLLECTIONS OF SECRETION FROM GASTRIC POUCH | |
|---|---|---|
| | Volume (Cc ) 30 Minute Periods | HCl (mEq/l) |
| *Antral pouch perfused with normal saline* | | |
| ½ | 0 5 | 0 |
| 1 | 0 5 | 0 |
| *Antral pouch perfused with liver extract* | | |
| 1½ | 1 3 | 0 |
| 2 | 3 0 | 21 |
| *Antral pouch perfused with normal saline* | | |
| 2½ | 1 8 | 60 |
| 3 | 1 6 | 68 |
| 3½ | 1 0 | 47 |
| 4 | 0 4 | 23 |
| 4½ | 0 2 | 3 |
| 5 | 0 2 | 0 |

perfused through the antrum in the same period of time In the meantime quantitative thirty minute collections are made from the indicator Heidenhain pouch these are continued for one hour after completion of the perfusion The substances used as standard chemical stimuli are 5 per cent ethyl alcohol and crude liver extract The liver extract is prepared by mixing one part of powdered dehydrated liver with ten parts of distilled water The solution is centrifuged and the clear supernatant is used as an antral perfusion

The isolated innervated antral pouch is highly susceptible to chemical stimuli (49) Crude liver extract causes a relatively prompt secretion of acid gastric juice from the indicator pouch usually with a latent period of less than thirty minutes (Table 2) The pH of crude liver extract is 6–6 2

When the pH of the liver extract is reduced to 1.2, perfusion of the isolated antrum under identical conditions results in no secretion of gastric juice by the indicator pouch (Table 3). Although a response to liver extract becomes less reliable as the pH is gradually lowered, it is unusual to find striking inhibition unless the pH is dropped to at least 1.5.

Alcohol has been found to be a potent stimulant for gastrin release even when very dilute (51, 52). Because of ease in preparation and handling

TABLE 3

EFFECT ON GASTRIC SECRETION OF THE pH OF ANTRUM PERFUSATE

| TIME SINCE START OF PERFUSION (HOURS ELAPSED) | COLLECTIONS OF SECRETION FROM GASTRIC POUCH: Volume (Cc.) 30 Min. Periods | Free HCl (C.U.) |
|---|---|---|
| *Isolated antrum irrigated with 0.9% NaCl* | | |
| ½ | 1.5 | 0 |
| 1 | 1.0 | 0 |
| *Isolated antrum irrigated with liver homogenate at pH 5.2* | | |
| 1½ | 2.5 | 14 |
| 2 | 1.5 | 18 |
| *Isolated antrum irrigated with 0.9% NaCl solution* | | |
| 2½ | 1.5 | 0 |
| *Isolated antrum irrigated with liver solution at pH 1.2* | | |
| 3 | 0.5 | 0 |
| 3½ | 0.5 | 0 |
| 4 | 1.0 | 0 |
| 4½ | 1.0 | 0 |
| 5 | 1.0 | 0 |
| 5½ | 1.5 | 0 |
| 6 | 0.5 | 0 |

this is the chemical stimulant most often used. When the pH of alcohol is reduced to 1.2–1.5, the same absence of stimulation is noted as occurs with acid liver extract (Table 4).

In more recent studies antral perfusion has been performed with liver extract and alcohol after altering the pH in the alkaline direction (50). No enhancement of the secretory response occurred. Motility tracings of the antrum made in the course of chemical stimulation revealed no change in contractions with either liver extract or alcohol as stimulants.

From these data it is apparent that the isolated innervated antrum is

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TABLE 2

EFFECT ON GASTRIC SECRETION OF LIVER EXTRACT IN ISOLATED ANTRUM

| Time since Start of Perfusion (Hours Elapsed) | Collections of Secretion from Gastric Pouch | |
|---|---|---|
| | Volume (Cc) 30 Minute Period | HCl (mEq/l) |
| *Antral pouch perfused with normal saline* | | |
| ½ | 0.5 | 0 |
| 1 | 0.5 | 0 |
| *Antral pouch perfused with liver extract* | | |
| 1½ | 1.3 | 0 |
| 2 | 3.0 | 21 |
| *Antral pouch perfused with normal saline* | | |
| 2½ | 1.8 | 60 |
| 3 | 1.6 | 68 |
| 3½ | 1.0 | 47 |
| 4 | 0.4 | 23 |
| 4½ | 0.7 | 3 |
| 5 | 0.2 | 0 |

perfused through the antrum in the same period of time In the mean time quantitative thirty minute collections are made from the indicator Heidenhain pouch these are continued for one hour after completion of the perfusion The substances used as standard chemical stimuli are 5 per cent ethyl alcohol and crude liver extract The liver extract is prepared by mixing one part of powdered dehydrated liver with ten parts of distilled water The solution is centrifuged and the clear supernatant is used as an antral perfusion

The isolated innervated antral pouch is highly susceptible to chemical stimuli (49) Crude liver extract causes a relatively prompt secretion of acid gastric juice from the indicator pouch usually with a latent period of less than thirty minutes (Table 2) The pH of crude liver extract is 6–6 2

Overdistention promptly produces retching negating the experiment and indicating the need for a smaller volume in subsequent studies of the same animal. During the period of distention the antrum is gently and continuously perfused with normal salt solution. The perfusate is changed to alter the pH of the antrum while the mechanical stimulus of the balloon is maintained at a constant pressure. Thirty minute collections of gastric secretion are made from the Heidenhain pouch.

TABLE 5

EFFECT OF ACID PERFUSION OF ANTRAL POUCH DURING CONSTANT MECHANICAL STIMULATION

| TIME SINCE START OF PERFUSION (HOURS ELAPSED) | COLLECTIONS OF SECRETION FROM GASTRIC POUCH | |
|---|---|---|
| | Volume (CC.) in 30-Minute Period | HCl (mEq.) |
| *Foley bag inflated and antrum perfused with 0.9% NaCl* | | |
| ½ | 4.0 | 0.00 |
| 1 | 10.5 | 0.33 |
| 1½ | 18.0 | 2.34 |
| 2 | 13.0 | 1.64 |
| 2 | 11.0 | 1.32 |
| *Perfusate changed to N/10 HCl* | | |
| 3 | 12.5 | 1.14 |
| 3½ | 4.5 | 0.39 |
| 4 | 7.0 | 0.27 |
| 4½ | 4.0 | 0.12 |
| 5 | 3.0 | 0.00 |
| *Perfusate changed to 0.9% NaCl* | | |
| 5½ | 3.5 | 0.02 |
| 6 | 6.5 | 0.39 |
| 6½ | 15.0 | 1.80 |

Mechanical stimulation of the isolated antrum by inflation of the balloon causes a prompt secretion of highly acid gastric juice from the indicator Heidenhain pouch usually within thirty minutes. If the antrum is perfused with N/10 HCl this secretory response is regularly blocked (Table 5). Sensitivity of the antrum to the concentration of HCl is presented in Table 6. Hydrochloric acid at a strength of N/20 (pH 1.3) easily blocks the mechanical stimulus whereas N/50 HCl with a pH of 1.7 is ineffectual. Nitric and sulfuric acids in similar concentrations are equally as effective as HCl indicating as would be expected that the important factor is the hydrogen ion concentration.

Perfusion of the antrum with an alkaline fluid—isotonic (1.3 per cent) sodium bicarbonate—has been found to enhance the mechanical stimulus

highly susceptible to chemical stimuli but that such stimulation can be completely blocked by reducing the pH of the perfusate to the level of 1.2–1.5

MECHANICAL STIMULATION OF THE ISOLATED ANTRUM

That mechanical factors might be important in the gastrin mechanism was suggested by the studies of Grossman *et al* (13) and by the observation that a pre-existing gastroenterostomy obviated the stimulatory effect of vagotomy in Heidenhain pouch dogs. The isolated vagally innervated gastric antrum has been found to be extremely sensitive to mechanical stimuli—so much so that even gentle perfusion with normal saline will often cause some secretory response. The method used as a standard stimulus is the inflation of a balloon within the isolated antrum. A Foley catheter is inserted into the antrum through the pyloric fistula and the balloon is inflated with water. The amount needed will vary from one experimental preparation to another; usually 15–25 cc suffices for strong stimulation

TABLE 4

EFFECT ON GASTRIC SECRETION OF ALCOHOL IN THE ISOLATED ANTRUM

| Time since Start of Perfusion (Hours Elapsed) | Collections of Secretion from Gastric Pouch | |
|---|---|---|
| | Volume (Cc) in 30-Minute Period | HCl (mEq/l) |
| *Antral pouch perfused with normal saline* | | |
| ½ | 0 | |
| 1 | 0 | |
| *Antral pouch perfused during one hour with 250 cc 5% alcohol (pH 6.1)* | | |
| 1½ | 3.[illegible] | 10 |
| 2 | 8.0 | 136 |
| *Antral pouch perfused with normal saline* | | |
| 2 | 9.5 | 140 |
| 3 | [illegible].5 | 139 |
| 3½ | 2.5 | 114 |
| 4 | 1.0 | 0 |
| *Antral pouch perfused during one hour with 250 cc 5% alcohol (pH 1.2)* | | |
| 4½ | 1.0 | 0 |
| 5 | 0 | |
| *Antral pouch perfused with normal saline* | | |
| 5½ | 1.5 | 15 |
| 6 | 0 | |
| 6½ | 0 | |

Overdistention promptly produces retching, negating the experiment and indicating the need for a smaller volume in subsequent studies of the same animal. During the period of distention the antrum is gently and continuously perfused with normal salt solution. The perfusate is changed to alter the pH of the antrum while the mechanical stimulus of the balloon is maintained at a constant pressure. Thirty minute collections of gastric secretion are made from the Heidenhain pouch.

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|---|---|---|
| | Volume (Cc.) 30-Minute Period | HCl (mEq.) |
| *Foley bag inflated and antrum perfused with 0.9% NaCl* | | |
| ½ | 4.0 | 0.00 |
| 1 | 10.5 | 0.33 |
| 1½ | 18.0 | 2.34 |
| 2 | 13.0 | 1.64 |
| 2 | 11.0 | 1.32 |
| *Perfusate changed to N/10 HCl* | | |
| 3 | 12.5 | 1.14 |
| 3½ | 4.5 | 0.39 |
| 4 | 7.0 | 0.27 |
| 4½ | 4.0 | 0.12 |
| 5 | 3.0 | 0.00 |
| *Perfusate changed to 0.9% NaCl* | | |
| 5½ | 3.5 | 0.02 |
| 6 | 6.5 | 0.59 |
| 6½ | 15.0 | 1.80 |

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TABLE 4

EFFECT ON GASTRIC SECRETION OF ALCOHOL IN THE ISOLATED ANTRUM

| Time St[illegible] (Ho[illegible] E[illegible]) | Collections of Secretion from Gastric Pouch: Volume (Cc) 30 Minute Period | HCl (mEq/l) |
|---|---|---|
| *Antral pouch perfused with normal saline* | | |
| ½ | 0 | |
| 1 | 0 | |
| *Antral pouch perfused during one hour with ? 0 cc 5 alcohol (pH 6 1)* | | |
| 1½ | 3 5 | 105 |
| 2 | 8 0 | 136 |
| *Antral pouch perfused with normal saline* | | |
| 2 | 9 5 | 140 |
| 3 | 5 5 | 139 |
| 3 | 2 5 | 114 |
| 4 | 1 0 | 0 |
| *Antral pouch perfused during one hour with ?50 cc 5 alcohol (pH 1 )* | | |
| 4½ | 1 0 | 0 |
| 5 | 0 | |
| *Antral pouch perfused with normal saline* | | |
| 5½ | 1 5 | 15 |
| 6 | 0 | |
| 6½ | 0 | |

perforce by an increase in antral motility These factors seem to indicate that the two mechanisms for initiating the gastrin response may be separate and distinct

## THE EFFECT OF LOCAL ANESTHETICS ON THE GASTRIN MECHANISM

The diffuse histological structure of the antral mucosa affords us no clue as to the cytologic origin of gastrin In contrast to other glandular struc

TABLE 7

EFFECT OF ALKALI IN ANTRAL POUCH DURING MECHANICAL STIMULATION

| Time Since Start of Perfusion (Hours Elapsed) | Collection of Secretion from Gastric Pouch | |
|---|---|---|
| | Volume (Cc ) 30-Minute Period | HCl (mEq ) |
| *Antrum perfused with saline* | | |
| ½ | 2 5 | 0 13 |
| 1 | 2 5 | 0 27 |
| 1½ | 2 0 | 0 19 |
| 2 | 2 5 | 0 23 |
| | | 0 82 |
| *Perfusion changed to* $1.3\%$ $NaHCO_3$ *(pH 8 3)* | | |
| 2½ | 2 5 | 0 23 |
| 3 | 3 5 | 0 35 |
| 3½ | 5 5 | 0 59 |
| 4 | 4 5 | 0 49 |
| | | 1 66 |

tures with both endocrine and exocrine secretions there are no separate cellular complexes in the antrum which might be exclusively responsible for gastrin manufacture Although the extrinsic nerves to the antrum are not essential for gastrin production the intrinsic neural plexuses seem to be more important Savitch (33) who incidentally was able to obtain acid secretion from the fundus of the stomach by applying food to the antrum found that this effect was abolished by prior cocainization of the antral mucosa Utilizing the isolated antral pouch preparation 2–5 per cent cocaine plus other topical anesthetic agents were applied to the antral mucosa by direct instillation Chemical and mechanical stimuli were then applied using the technics outlined above In addition gastric secretion was stimulated by means of subcutaneous histamine or insulin induced hypoglycemia

in most experiments An ineffective mechanical stimulus can be made effective by switching the perfusate from normal salt solution to sodium bicarbonate An adequate mechanical stimulus is potentiated by switching to an alkaline perfusate (Table 7)

Unlike chemical stimulation of the antrum mechanical stimulation results in a constant increase in antral motility This was largely an increase in the amplitude of contractions although some increase in frequency was

TABLE 6

EFFECT OF DILUTING ACID PERFUSATE WHILE MAINTAINING MECHANICAL STIMULATION

| TIME SINCE START OF PERFUSION (HOURS ELAPSED) | COLLECTION OF SECRETION FROM GASTRIC POUCH | |
|---|---|---|
| | Volume (CC) 30-Minute Period | HCl (mEq/l) |
| *Antral pouch perfused with normal saline* | | |
| ½ | 16 5 | 99 |
| *Perfusate changed to N/20 HCl (pH 1 3)* | | |
| 1 | 3? 0 | 3? |
| 1½ | 9 0 | 60 |
| 2 | 5 0 | 32 |
| 2½ | 0 8 | 0 |
| 3 | 8 0 | 0 |
| *Perfusate changed to normal saline* | | |
| 3½ | 15 0 | 0 |
| 4 | 24 0 | 36 |
| *Perfusate changed to N 50 HCl (pH 1 7)* | | |
| 4½ | 23 5 | 60 |
| | 32 5 | 34 |
| 5½ | 18 5 | 56 |
| 6 | 19 2 | 42 |
| 6 | 10 8 | 83 |

also noted This persisted for exactly the period of secretory response Tiny doses of anticholinergic drugs blocked the motility increase and also blocked gastrin release

These studies are interpreted as demonstrating strong stimulation of the gastrin mechanism by mechanical stimuli Mechanical stimulation can be readily and completely blocked by the simultaneous perfusion of the antrum with an acid solution The critical pH is between 1 3 and 1 7 Unlike chemical stimulation a mechanical stimulus is enhanced by alkaline perfusion of the antrum and also mechanical stimulation is accompanied

environment by other means thus stressing the specific influence of an trum on gastrin release For example one study (49) showed that the feeding of an animal with a denervated gastric pouch and a totally iso lated antrum activated the intestinal phase of secretion and this phase was not inhibited when the antrum was perfused with N/10 HCl Another investigation used the continuous histamine technic to stimulate gastric secretion after a plateau of secretion was reached the antrum was per fused with N/10 HCl secretion was not inhibited significantly or if a de crease did occur it usually followed a prolonged latent period In another case an experimental dog with an isolated antrum and a gastric fistula se creted from the main stomach in response to insulin induced hypogly cemia Perfusion of the antrum with acid had no suppressive effect on the gastric secretory response From these studies it was concluded that the effect of acid in the antrum was specific in its inhibitory properties for gas tric secretion resulting from the antral hormone gastrin Since other inhibi tory substances such as enterogastrone will inhibit gastric secretion from whatever stimulus this was considered as constituting evidence against an antisecretory hormone and in favor of some local chemical interference with gastrin formation or release

On the other hand Harrison *et al* (16) reported studies providing in direct evidence that an antisecretory hormone may indeed be produced by the antrum In seven dogs prepared with indicator Heidenhain pouches the distal half of the antrum was transplanted into the transverse colon after the method described by Dragstedt *et al* (5) Gastroduodenal con tinuity was restored with a Shoemaker Billroth I end to end anastomosis After a period of control collections from the Heidenhain pouch the re maining antral segment was resected from between the body of the stomach and the duodenum leaving the colon implant untouched In all seven animals collections of secretion from the Heidenhain pouch were larger after this procedure indicating that the antral remnant in normal continuity exerted some suppressive influence on the portion of the antrum transplanted into the colon

More recently Jordan and Sand (18) have provided direct evidence favoring an antisecretory hormone In dogs prepared with a Heidenhain pouch the antrum was isolated from continuity and divided longitudinally into two completely separated antral pouches Each was fistularized to the skin one receiving its blood supply from the lesser curvature structures and the other from the epiploic vessels (Fig 9) One antral pouch was perfused with 10 per cent alcohol until a brisk secretory response was secured from the Heidenhain pouch Then the second antral pouch was perfused with N/10 HCl After a rather long latent period sometimes as long as two and one half hours the secretory response from alcohol stimu lation was suppressed in 15 of 20 experiments (Fig 10)

Cocaine in strengths of 2-5 per cent was found to block completely both chemical or mechanical stimulation of the isolated antrum (Table 8) The response to alcohol perfusion and to balloon distention was also prevented Stimulation by histamine or insulin hypoglycemia was not inhibited

In more recent experiments (34) xylocaine pontocaine and nupercaine have been found to produce the same effect although not so reliably or drastically as in the case of cocaine Since these topical anesthetics are quite distinct from cocaine chemically it seems unlikely that the effect noted was due to anything other than the anesthetic properties of these drugs Certainly this phenomenon seems to indicate the importance of the intramural nervous tissue of the antrum in the performance of its endocrine function

## DOES ACID IN THE ANTRUM PRODUCE AN ANTISECRETORY HORMONE?

The inhibitory effect of acid upon gastrin production has been studied extensively The experimental emphasis has often been on creating an acid

TABLE 8

EFFECT OF LIVER HOMOGENATE IN ANTRAL POUCH FOLLOWING COCAINIZATION

| TIME SINCE START OF PERFUSION (HOURS ELAPSED) | COLLECTION OF SECRETION FROM GASTRIC POUCH | |
|---|---|---|
| | Volume (Cc) 30-Minute Periods | Free HCl (C U) |
| *Isolated antrum irrigated with 0 9% NaCl* | | |
| ½ | 1.0 | 0 |
| 1 | 1.0 | 0 |
| 1½ | 2.0 | 0 |
| 2 | 3.0 | 0 |
| 2½ | 2.0 | 0 |
| 3 | 1.0 | 0 |
| 3½ | 1.0 | 0 |
| 4 | 2.0 | 0 |
| *Isolated antrum irrigated with 2% cocaine and then with liver homogenate* | | |
| 4½ | 1.0 | 0 |
| *Isolated antrum irrigated with liver homogenate* | | |
| 5 | 1.0 | 0 |
| 5½ | 1.5 | 0 |
| 6 | 3.0 | 0 |
| 6½ | 2.0 | 0 |
| 7 | 3.0 | 0 |
| 7½ | 2.0 | 0 |
| 8 | 1.0 | 0 |

environment by other means thus stressing the specific influence of antrum on gastrin release For example one study (49) showed that the feeding of an animal with a denervated gastric pouch and a totally isolated antrum activated the intestinal phase of secretion and this phase was not inhibited when the antrum was perfused with N/10 HCl Another investigation used the continuous histamine technic to stimulate gastric secretion after a plateau of secretion was reached the antrum was perfused with N/10 HCl secretion was not inhibited significantly or if a decrease did occur it usually followed a prolonged latent period In another case an experimental dog with an isolated antrum and a gastric fistula secreted from the main stomach in response to insulin induced hypoglycemia Perfusion of the antrum with acid had no suppressive effect on the gastric secretory response From these studies it was concluded that the effect of acid in the antrum was specific in its inhibitory properties for gastric secretion resulting from the antral hormone gastrin Since other inhibitory substances such as enterogastrone will inhibit gastric secretion from whatever stimulus this was considered as constituting evidence against an antisecretory hormone and in favor of some local chemical interference with gastrin formation or release

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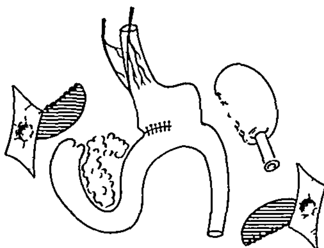


Fig. 9.—Double antral pouches in dog with Heidenhain pouch. (From Jordan and Sand 18.)

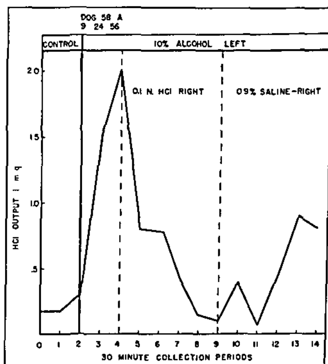



Fig. 10.—Suppression of gastrin response by perfusing second antral pouch with acid. (From Jordan and Sand 18.)

The experiment of Harrison and his colleagues has been difficult to repeat. We have prepared four dogs using Harrison's technic with the exception of transplanting the proximal half of the antrum into the colon while maintaining the distal half in gastroduodenal continuity. In the four dogs thus prepared resection of the antral remnant which remained in continuity was followed by no change in secretion of gastric juice by the Heidenhain pouch (41).

Greenlee *et al.* (12) have reported striking inhibition of gastric secretion by the administration of intravenous secretin. Like the inhibition of

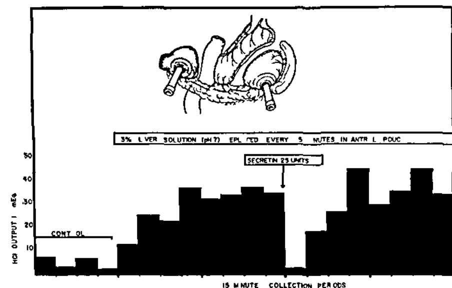



Fig. 11.—Effect of secretin on the gastrin mechanism in dogs with antral and Heidenhain pouches.

gastric secretion noted in the experiments with acid perfusion of the isolated antrum, inhibition with secretin seems to be completely specific for gastric secretion of antral origin. Gastric secretion from the intestinal phase, histamine stimulation, or vagal stimulation as produced by insulin hypoglycemia have all been uninfluenced by secretin administration. A typical protocol is presented in Figure 11.

## IS SECRETIN THE INHIBITORY HORMONE OF THE ANTRUM?

Teleologically it would seem desirable to assume that contact of acid with the antrum would release secretin which in turn would inhibit further function of the gastric phase of gastric secretion and would at the same time stimulate pancreatic secretion in preparation for the influx of gastric

content into the duodenum Is it possible that such a mechanism exists and that the antisecretory hormone liberated by contact of acid with antral mucosa is in effect secretin? It has been known for a long period that the mucosa of the antrum contains secretin for crude extracts of the antrum will stimulate not only gastric secretion but also pancreatic secretion With more extensive purification the effect on the pancreas is lost indicating that gastrin itself does not affect pancreatic secretion (23)

To test this hypothesis three dogs were prepared each with an isolated pouch of the gastric antrum At a second stage a pancreatic fistula was created after the method of Dragstedt Montgomery and Ellis (4) Collections of pancreatic juice were made while the antrum was perfused with various solutions (40)

In eight experiments the antrum was perfused for two and one half to four hours with N/10 HCl There was no change in pancreatic secretion in any experiment Perfusion of the antrum with protein hydrolysates liver extract 5 per cent alcohol and soap solution stimulated gastric secretion but had no effect on pancreatic secretion In all three dogs intravenous secretin stimulated pancreatic secretion

Therefore we have been unable to obtain experimental evidence in favor of the hypothesis that secretin is the inhibitory hormone of the antrum Like the primary question—whether such a second antral hormone exists or not—it remains unanswered

## THE ANTRUM EXCLUSION OPERATION MECHANISM OF ITS FAILURE

In patients with duodenal ulcer the antrum exclusion operation is popularized by Finsterer and Devine after von Eiselsberg s original description is followed by an excessively high incidence of marginal ulcer formation at the gastrojejunal stoma This clinical observation which was instrumental in reawakening interest in the antrum of the stomach can now be fully explained by the results of the experiments performed To exemplify these findings four dogs were prepared with Heidenhain pouches Then utilizing the acid cuff principle described by Oberhelman *et al* (27) an antrum exclusion operation was performed including a large segment of acid secreting mucosa with the excluded antrum The proximal gastric stump was anastomosed to the jejunum (Fig 12) This in essence is the operation originally described by von Eiselsberg in which actually no stomach is removed at all the stomach is merely transected in its mid portion This is also the alkalizing operation described by Devine (Fig 13)

In the usual fashion of the laboratory these animals were maintained on a constant diet with sodium chloride supplement as indicated After a

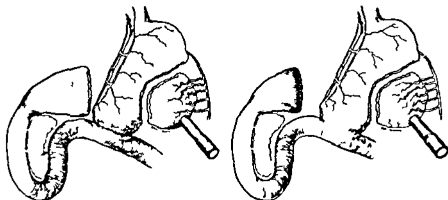


Fig 12 —Heidenhain pouch with *left* exclusion of antrum along with large cuff of acid secreting stomach and *right* after resection of the acid cuff from excluded antrum

Fig 13 —The alkalizing operation of Devine 1 distal end of gastric fundus anastomosed to jejunum 2 excluded gastric antrum 3 duodenal ulcer *in situ* 4 gastrohepatic ligament and retroperitoneum (From Devine 2 )

long period of observation reoperation was performed and the acid secreting cuff of tissue was excised from the excluded antrum using microscopic sections to insure accurate demarcation In no way was the Heidenhain pouch the main stomach or the gastrojejunal anastomosis disturbed This end result was the operation described and popularized by Finsterer and most widely used by surgeons throughout the world in the early decades of this century Finsterer called it "resection for exclusion" where a sleeve is excised from the mid portion of the stomach and as a result the antrum is infolded and excluded without adjacent acid secreting tissue

When the four dogs were studied through a subsequent observation period (53) during which they were on exactly the same dietary program there was a striking increase in secretion from the Heidenhain

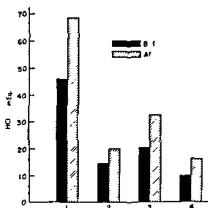



Fig 14 —Effect of excising acid secreting mucosa from the excluded antrum

pouch in all four (Fig 14) In three of the dogs secretion nearly doubled and in two the resistive powers of the mucous membrane lining the pouch were overwhelmed and peptic ulceration resulted

It can therefore be concluded that the high ulcer recurrence rate after the exclusion gastrectomy is the result of excessive production of acid gastric juice by the remaining body of the stomach Food substances reflux through the afferent jejunal loop and duodenum and eventually through the pylorus into the excluded antrum En route any acid present has been thoroughly neutralized by the alkaline duodenal fluids The neutral food substances chemically excite the antrum to release gastrin which in turn stimulates the secretion of acid gastric juice by the body of the stomach However the body of the stomach is now remote from the stimulated antrum so that the pH of the antrum does not fall as is the case when there is normal continuity Thus the normal physiological device—perhaps an antisecretory hormone liberated by the presence of acid in the antrum—

is completely negated by the alterations in anatomy wrought by surgery This delicate balance normally functions as accurately as a thermostatic regulator in a heating system and is sensitive to variations in pH as small as 0 2

The importance of maintaining the antrum in its normal relationship to acid secreting gastric tissue is therefore apparent and the practical lesson for the surgeon is obvious Where gastric resection is used the antrum or at least its mucous membrane must be completely excised and not excluded When vagotomy is used to remove the exaggerated nervous phase of gastric secretion so characteristic of the duodenal ulcer patient it is essential that an adequate drainage procedure be utilized Otherwise the stomach with markedly lower acidity will fail to empty properly and chronic stimulation of the antrum will occur from both chemical and mechanical influence of the retained food substances This will substitute a hyperactive antral or digestive phase of acid production for the preexisting hyperactive interdigestive nervous phase

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# 4 *Clinical Importance of the Gastric Phase of Secretion*

The evidence as cited in chapter 2 indicates that most duodenal ulcers are due to a hypersecretion of gastric juice of nervous origin which is abolished by complete division of the vagus nerves to the stomach It has been suggested however that in some patients hypersecretion of gastric juice may be of antral origin rather than vagal and that an attempt should be made to differentiate these patients and thereby to apply treatment appropriate to the cause Schoen and Griswold (1) in 1953 found that the gastric secretory characteristics as measured by the histamine test showed a predominantly humoral response in about 5 per cent of ulcer patients and for these they recommended subtotal gastrectomy Actually one cannot conclude that antrum hyperfunction exists in these patients since histamine is a direct cellular stimulant measuring the secretory sensitivity of the gastric mucosa and not the gastric phase of secretion Thus there is little evidence that the antral phase of gastric secretion plays any role in the etiology of uncomplicated duodenal ulcer

## GASTRIC ULCER AFTER VAGOTOMY ALONE FOR DUODENAL ULCER

When vagotomy was introduced in the University of Chicago Clinics in 1943 it was not combined with a gastric drainage procedure During the ensuing years our interest was aroused by the development of new benign gastric ulcers in six patients treated by vagotomy alone This interesting complication had also been observed by others Our first case was observed in 1948 it occurred in the first patient ever subjected to transthoracic vagotomy for duodenal ulcer

**Case History** W B A 63 year old male underwent a transthoracic vagotomy in January 1943 for duodenal ulcer X rays revealed high grade pyloric stenosis with a huge ulcer crater in the base of the duodenal bulb Preoperative twelve hour night secretion measured 1 160 ml with a free acidity of 65 clinical units or a total of 75 mEq of free HCl in the complete collection Postoperative twelve hour night secretion measured 310 ml with a free acid of 58 clinical units or 18 mEq of free HCl a reduction of 76 per cent Following surgery he became asymptomatic and remained so except for mild symptoms of gastric stasis until four years postvagotomy when he again noted gnawing pain in the epigastrium occurring after meals and occasionally at night Symptoms were relieved by food soda and vomiting X ray revealed a huge ulcer crater on the lesser curvature of the stomach just above the angulus and marked deformity of the base of the duodenal bulb and pyloric channel without evidence of crater Twelve hour night secretion measured 620 ml with no free acid and the response to insulin hypoglycemia was negative On April 11 1947 a subtotal gastric resection was performed Pathological diagnosis showed a benign gastric ulcer and the scar of a duodenal ulcer He remained asymptomatic until his death in August 1952 following a leg amputation for a diabetic condition

Thus a new benign gastric ulcer occurred in this patient even though the original duodenal ulcer had completely healed and in spite of a persistent reduction in the twelve hour night gastric secretion and a negative response to insulin hypoglycemia The question naturally arose why such a gastric ulcer should develop The answer was later found through laboratory experiments relating to the physiology of the pyloric antrum in gastric secretion

In Dr Woodward s chapter the mechanisms of antrum stimulation have been clearly summarized These include local stimulation by food peristalsis and distention The importance of distention and peristalsis as mechanisms in the release of gastrin was demonstrated in a fundamental experiment in which the isolated denervated antrum was transplanted into the colon as a diverticulum A marked and persistent hypersecretion of gastric juice of antral origin was produced in this manner This profound stimulation of gastric secretion induced by distention was also observed experimentally (2) and is illustrated in Figure 1

IMPORTANCE OF DISTENTION IN THE RELEASE OF GASTRIN

A large Heidenhain pouch from the greater curvature of the stomach was constructed in the dog D 238 with a nylon plastic cannula introduced into the pouch for the quantitative collection of gastric secretion After the animal had completely recovered from the operation the gastric juice secreted during each twenty four hour period was collected its volume measured and the concentration of free HCl determined by titration with Topfer s reagent The total output of free HCl was calculated in milli

equivalents Preliminary operative procedures involved transplantation of the entire antrum into the colon as a diverticulum and then a partial resection of the transplanted antrum Following these procedures the average daily output of free HCl from the Heidenhain pouch over a twenty five-day period was 29 mEq (Fig 1 *first drawing*) The animal was again operated upon, and this time the antral transplant was carefully separated from all its original blood supply now deriving its nourishment from new blood vessels coming from the colon At this time the portion of the colon containing the antral transplant was converted into a Thiery Vella

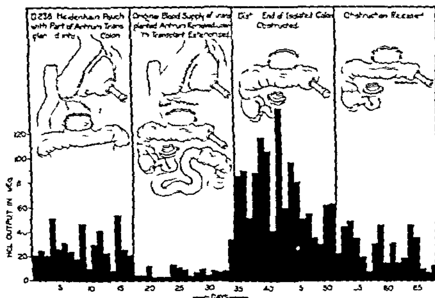



Fig 1 —The effect of distention on the denervated transplanted antrum

fistula, open at both ends (Fig 1 *second drawing*) A nylon plastic cannula was introduced into the distal end of the colon loop containing the antral diverticulum which permitted irrigation of this segment of the colon to make certain that it contained no trace of food or fecal material During this observation period the average daily output of free HCl fell to 10 mEq Next, the distal end of the isolated colon was obstructed by placing a cap on the nylon cannula the proximal opening was left open (Fig 1 *third drawing*) This maneuver resulted in a marked hypersecretion of gastric juice from the Heidenhain pouch averaging around 70 mEq per day When the cap was removed, allowing the escape of thin mucoid colonic secretions the average daily output of free HCl was greatly reduced (Fig 1 *last drawing*)

Since nothing was introduced into the colon segment, it seemed likely that the intraluminal tension developed by peristalsis in the isolated segment of the colon in response to the obstruction proved a most effective stimulus for the release of gastrin from the antrum It is also of interest that this secretion continued even though the original blood supply to the antrum had been divided

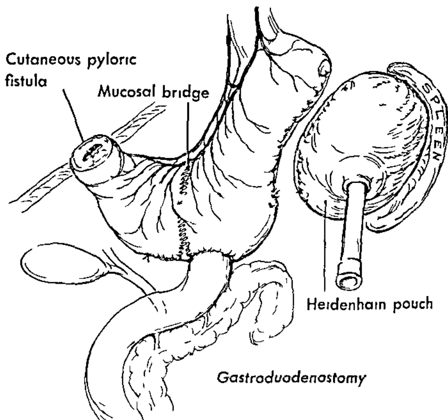



Fig 2 —Exclusion of the gastric antrum with innervation intact and Heidenhain pouch

*IMPORTANCE OF PERISTALSIS IN THE RELEASE OF GASTRIN*

In another more recent experiment the significance of antrum peristalsis in the release of gastrin was emphasized (3) After the construction of a Heidenhain pouch the antrum was excluded from the body of the stomach by a mucosal bridge leaving intact the entire seromuscular layer lesser curvature structures and nerve supply The pylorus was divided and a cutaneous fistula constructed from the proximal end Gastrointestinal continuity was re established by gastroduodenostomy (Fig 2) Following total exclusion of the innervated antrum the quantitative daily

output of free HCl remained unchanged from the Heidenhain pouch in four animals (Table 1) Thus in spite of its complete exclusion from the gastrointestinal tract the preservation of its innervation permitted the antrum to undergo vigorous periodic contractions The contractions occurred in response to feeding, during which peristalsis was transmitted from the body of the stomach by intact intramural autonomic reflexes they could also be induced by insulin hypoglycemia with its consequent direct stimulation of vagal motor fibers running to the antrum They were abolished however by withholding food (Fig 3) As a result of this experiment it was apparent that when antrum motility was preserved there was a marked secretory response

TABLE 1

EFFECT OF EXCLUSION OF THE INNERVATED ANTRUM ON QUANTITATIVE DAILY GASTRIC SECRETION

| Dog | Mean 24-Hour Secretion (mEq HCl) | |
|---|---|---|
| | Control (30-Day Collection) | Antrum Excluded (30-Day Collection) |
| D 800 | 34 | 27 |
| D 983 | 23 | [illegible] |
| D 984 | 35 | 38 |
| D 997 | 25 | 21 |

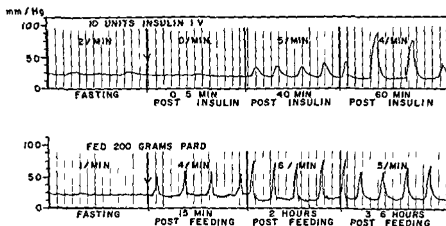



FIG 3 —Antrum motility in response to feeding and insulin hypoglycemia

IMPORTANCE OF GASTRIC STASIS IN THE RELEASE OF GASTRIN

These fundamental experiments on the gastric antrum led to a better understanding of the development of gastric ulcer following simple vagotomy. One of the most important experiments was performed in two laboratories but independently (4, 5). Heidenhain pouches devoid of vagus innervation were prepared in dogs and secretory characteristics were measured during control periods. The vagus nerves to the main stomach were then severed transthoracically. Postvagotomy quantitative collections of gastric juice were resumed and to our surprise a great increase in the secretion of gastric juice from the Heidenhain pouch was consistently observed (Fig. 4). Resection of the antrum abolished the stimulating effect of vagotomy on secretion from the Heidenhain preparation, indicating that the increase in gastric secretion had been mediated through the antrum (Fig. 5); it was also found that a low lying gastroenterostomy was effective (Fig. 6). This increase in the humoral mechanism of secretion was thought to be due to stasis of food in the stomach as a result of decreased gastric tonus and motility caused by vagotomy. In addition, since the quantity of gastric juice produced by the main stomach was actually reduced by vagotomy, the inhibitory influence of acid upon the antral mucosa was partially abolished, permitting production of an increased amount of gastrin. It was likely that the more important factor accounting for this increase in secretion from the Heidenhain pouch was the postvagotomy retention of food in the stomach, resulting in prolonged contact of food with the antral mucosa and hyperfunction of the gastric phase of secretion. However, it must be remembered that a favorable pH must be present for the antrum to function; this tends to be toward the alkaline end of the scale.

IMPORTANCE OF GASTRIC ACIDITY IN THE RELEASE OF GASTRIN

In another experiment using a Heidenhain pouch, the acid secreting portion of the main stomach was removed by resecting the corpus and fundus (Fig. 7). Gastrointestinal continuity was re-established by an esophagoantrostomy. Similarly again an increase in gastric secretion was obtained from the Heidenhain pouch. The factors responsible for this stimulation were believed to be twofold. With the reduction in the amount of acid in the antrum, antral inhibition had been abolished, allowing a greater quantity of gastrin to be produced. And there was also an increase in antral distention as a result of the defect in its motility, since transecting the stomach was the equivalent of a vagotomy to the antrum and pylorus.

That this hypersecretion of gastric juice was of clinical importance was recently emphasized by Smith, Moulder and Adams (6). They reported

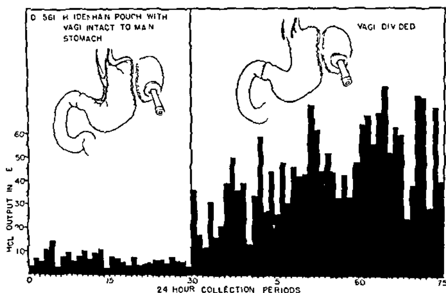



Fig 4 —Effect of vagotomy on gastric secretion in Heidenhain pouch dog

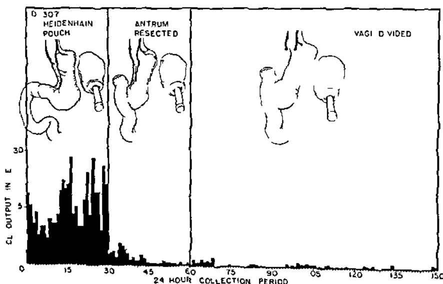



Fig 5 —Effect on gastric secretion of vagotomy in Heidenhain pouch dog with antrum resected

FIG 6 —Effect of vagotomy on gastric secretion in Heidenhain pouch dog with gastro-enterostomy

FIG 7 —Effect of fundusectomy on gastric secretion in Heidenhain pouch dog

four cases of gastric ulcer following cardioesophageal resection for carcinoma. It appeared that these ulcers were of humoral origin due to stasis of stimulating substances in the gastric antrum following the transection since two were clearly relieved by gastroenterostomy drainage procedures.

EFFECT OF PYLORIC STENOSIS ON GASTRIC SECRETION

In many patients treated for duodenal ulcer by vagotomy various degrees of pyloric stenosis with stasis of gastric contents occurred. Experimental production of pyloric obstruction in dogs produced hypersecretion of gastric juice from the denervated Heidenhain pouch (7). Similar findings had been reported earlier by Ivy, Droegemueller and Meyer (8) in 1927. In our experiments pyloric stenosis was produced either by wrapping narrow bands of cellophane around the duodenum just distal to the pylorus, securing these just tight enough to hold them in place, or by excising a diamond shaped portion of pyloric musculature from the antral wall, suturing the defect so as to create obstruction (Fig. 8). Following these procedures a prolonged increase in gastric secretion from the pouch was observed. One could infer that the stenosis caused increased gastric motility, that it increased tension within the antrum and caused prolonged contact between the antral mucosa and stimulating substances in the food. It is of interest that multiple gastric ulcers developed in one animal subsequent to pyloric stenosis (Fig. 9).

EXPERIMENTAL PRODUCTION OF GASTRIC ULCER

The expectation that vagotomy by delaying gastric emptying would alter the site of histamine induced ulceration prompted Brasher to perform the following experiment. Animals were subjected to bilateral transthoracic vagotomy and following a three week recovery period were given daily injections of histamine in wax and petrolatum. A comparable series of control dogs was not operated but received only the histamine preparation during the observation period. The daily dose of histamine used was one which produced a secretion of gastric juice of about the same magnitude as that which occurred in antral hyperfunction. After eight to ten weeks the animals were sacrificed and autopsies were performed. Peptic inflammation or mucosal erosions were more common than localized chronic ulcers with the dose of histamine used. There was a significant difference in the location of the peptic lesions in the two series: gastric lesions were found only in the vagotomized group but duodenal lesions were present in both groups. Although recent work by Kinluk and Merendino (10) suggests that the gastric mucosa is more resistant to acid pepsin digestion than is the duodenal mucosa, this cannot be the only factor in determining the site of ulceration. It would appear from our experiment that if gastric

emptying is delayed by vagotomy while the secretion of gastric juice is maintained by histamine the site of peptic ulceration is altered with an increase in gastric lesions

Several important clinical observations supported our experimental studies on the etiology of gastric ulcer following vagotomy Especially convincing were the studies of Huber and Huntington (11) in which they

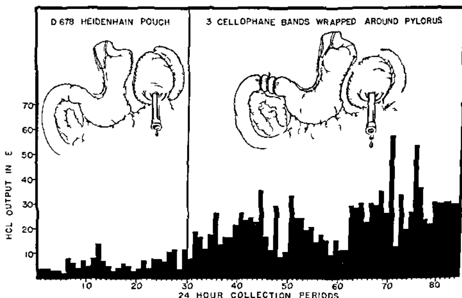



FIG 8 —Effect of pyloric obstruction on gastric secretion in Heidenhain pouch dog

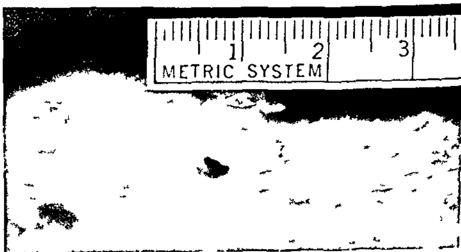



FIG 9 —Several small gastric ulcers located on the greater curvature of the stomach

demonstrated the appearance of gastric ulcers in patients where previous duodenal ulcers had produced gastric retention from pyloric stenosis (Fig 10) In our series of 158 patients with duodenal ulcer treated by vagotomy alone six subsequently developed a new benign gastric ulcer and two developed erosive hemorrhagic gastritis (12) This incidence of gastric ulcer was certainly much higher than seen in the normal population and it was a complication reported by many others

In summary when vagotomy alone was employed in the treatment of duodenal ulcer stasis of food as a result of deficient gastric peristalsis occurred resulting in a hypersecretion of gastric juice of antral origin and

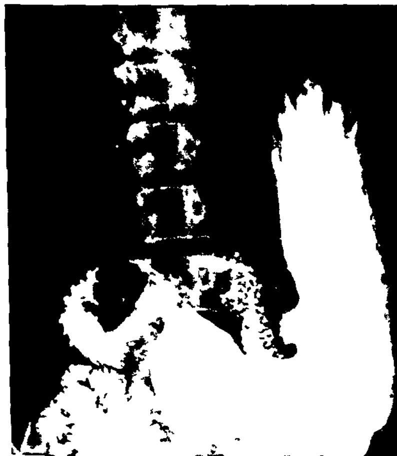


FIG 10—*Case I* Three years later the duodenal deformity is still present along with a large ulcer of the stomach (From Frank Huber and Charles G Huntington Gastric Retention and Gastric Ulcer *Amer J Roentgenol* 60 82 1948 Reprinted by permission of the authors and the *American Journal of Roentgenology* )

*an increased incidence of gastric ulceration Pyloric stenosis if present* caused a hypermotility of the stomach further enhancing the antral or humoral phase of gastric secretion As a result of these complications vagotomy without a drainage procedure was abandoned in the treatment of duodenal ulcer

## GASTRIC ULCER AFTER VAGOTOMY AND GASTROENTEROSTOMY FOR DUODENAL ULCER

During a recent analysis of the results of vagotomy and gastorenterostomy in the treatment of duodenal ulcer our interest was focused on those patients developing gastrojejunal ulceration in spite of a complete vagotomy as evidenced by a negative response to insulin hypoglycemia A typical case is described below

***Case History*** *M W This 54 year old insurance salesman underwent a trans* abdominal supradiaphragmatic vagotomy and posterior gastroenterostomy for a stenosing duodenal ulcer in January 1947 Preoperative twelve hour nocturnal secretion measured 1 100 ml with a free acidity of 51 clin cal units or 56 mEq of free HCl During the postoperative period the twelve hour nocturnal secretion measured 275 ml with no free acid and a negative response to insulin hypoglycemia was obtained Following release he gained in weight and remained well except for occasional distention and diarrhea X rays in February 1950 revealed a functioning gastroenterostomy and persistence of the previously demonstrated pyloric stenosis In March and December 1952 he noted tarry stools and a diagnosis of gastrojejunal ulcer was made At this time his twelve hour night secretion measured 214 ml with no free acid and his insulin test remained negative Thus in spite of a complete vagotomy this patient developed recurrent ulceration with hemorrhage some six years after his original operation

*The explanation of this unusual complication remained obscure until* further experimentation in animals shed light on its etiology Although as previously shown section of the vagus nerves resulted in gastric stasis with hyperfunction of the gastric or antral phase of secretion a drainage procedure such as gastroenterostomy should prevent this complication Since the vagotomy in this and similar cases was shown to have been complete our attention was then directed to the gastroenterostomy procedure Previous investigations in our laboratory had demonstrated that the Mann Williamson procedure for the production of experimental stomal ulcers regularly *caused a hypersecretion of gastric juice* (13) These studies prompted us to investigate the effect of certain types of gastroenterostomy in dogs on the secretion of gastric juice (14)

### EFFECT OF GASTROENTEROSTOMY ON GASTRIC SECRETION

Heidenhain pouches were prepared in dogs and after control studies had been obtained gastrojejunostomies were performed The anastomosis was

made either on the anterior or posterior wall of the stomach and varied in location from the pyloric antrum to the lower body of the stomach The results established the fact that gastroenterostomy produced a sustained increase in gastric secretion varying between 30 and 140 per cent of the initial value This increase in secretion occurred with both anterior and posterior wall anastomoses provided that the stoma was constructed in the body of the stomach (Fig 11) The finding that a similar gastroenterostomy did not stimulate gastric secretion if the antrum of the stomach had been resected suggested that this hypersecretion was of antral origin (Fig

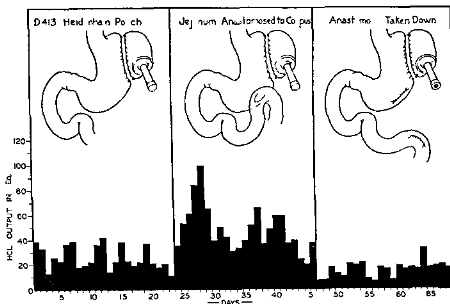



Fig 11 —The effect of gastroenterostomy on gastric secretion

12) In addition it was observed that gastrojejunostomy did not increase gastric secretion if the stoma was placed in the antrum of the stomach (Fig 13) Similar studies were also preformed by Kanar *et al* (15) in 195. They found that an increase in gastric secretion from the Heidenhain pouch in animals occurred irrespective of the position of the gastroenteric stoma on the stomach However they also reported that the anastomosis in the lower portion of the stomach produced a more pronounced stimulating effect The difference in the results of these two separate studies has subsequently been clarified by Stevenson *et al* (16) and by Woodward *et al* (18) on the basis of the size of the stomas produced since this factor varied in the two experimental studies It was shown that little or no increase in gastric secretion occurred when the gastroenterostomy was

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Heidenhain pouches were prepared in dogs and after control studies had been obtained gastrojejunostomies were performed The anastomosis was

placed in the antrum if the size of the stoma was limited to 2 cm However when the stomal diameter was increased a low lying gastrojejunostomy also produced a marked increase in gastric secretion probably as a result of reflux of alkaline secretions augmenting the gastrin mechanism

A tentative explanation of this stimulating effect of gastrojejunostomy when placed in the body of the stomach is that a high lying gastrojejunostomy either decreases the acid inhibition of gastrin release by draining away the acid secretions of the body and fundus before they come in contact with the antral mucosa or that it decreases the acidity of the gastric content as a result of reflux of alkaline duodenal juices through the stoma Thus a high lying gastrojejunostomy in itself stimulated gastric secretion via the antral mechanism

EXPERIMENTAL PRODUCTION OF STOMAL ULCER

As previously demonstrated a hypersecretion of gastric juice of humoral origin followed vagotomy or pyloric stenosis and occasionally resulted in gastric ulcer formation in the experimental animal In the above experiment it was shown that a high lying gastrojejunostomy also had a stimulating effect on the gastric phase of secretion The following study (18) was designed to determine if a hypersecretion of gastric juice of antral origin would produce stomal ulcers in experimental animals Transplantation of the antrum into the colon as a diverticulum was the method selected for producing hyperfunction of the antrum Intestinal continuity was re established by anastomosing the upper cut end of the stomach to the side of the jejunum (Fig 14) Following recovery from the operation the animals were maintained on a stock diet For two weeks they remained in excellent condition but subsequently developed anorexia or refused food altogther Typical large progressive gastrojejunal ulcers developed in five out of six animals in from three to twelve weeks These experimental ulcers displayed the characteristics of hemorrhage progression and perforation as seen in clinical lesions (Fig 15) It should be mentioned that spontaneous peptic ulcers have rarely appeared in dogs and in our experience have never been seen following gastroduodenostomy unless the alkaline secretions of the duodenum were deviated from the anastomosis or as shown above a hypersecretion of gastric juice was produced

In reviewing the results of vagotomy and gastroenterostomy during the period from 1943 to 1955 we found twenty eight patients or 5 8 per cent who developed a marginal gastrojejunal ulcer Eight of these patients displayed persistent reduction in the twelve hour nocturnal gastric secretion and a negative response to insulin hypoglycemia so that it may be assumed that the vagotomy was physiologically complete and the nervous phase of gastric secretion completely abolished While hypersecretion of

Fig. 12.—The effect of gastroenterostomy on gastric secretion after removal of the antrum

Fig. 13.—The effect of gastroenterostomy near the pylorus on gastric secretion

gastric juice of humoral origin could account for recurrent ulceration following vagotomy alone it was not readily apparent how this could account for marginal ulceration in these patients since a gastroenterostomy had been done to prevent stasis *However when these cases were carefully* reviewed two important facts were disclosed First it was observed from X ray studies that all eight patients had moderate to high grade obstruction as a result of pyloric stenosis which had existed preoperatively Pyloric stenosis as shown earlier produces a hypersecretion of gastric juice of humoral origin in experimental animals Second it was observed that the gastroenterostomy stomas had been placed either opposite the incisura or at the midfundus of the stomach in all cases None appeared to be located in the pyloric antrum Most of these patients had been operated upon early in our experience with vagotomy when little attention was directed toward positioning of the stoma near the pylorus

We have pointed out that high lying gastroenterostomy did not overcome the stasis that existed in the antrum following vagotomy to the main stomach in Heidenhain pouch dogs Therefore it was readily apparent that stasis of food in the pyloric antrum of these patients could lead to a hypersecretion of gastric juice of humoral origin as a result of a combination of factors These included stenosis decreased gastric motility as a result of the vagotomy and a high lying gastroenterostomy which failed to empty the stomach adequately and which in itself caused a hypersecretion of gastric juice of antral origin The antral stasis that existed in these patients is illustrated in Figure 16 These studies were performed by feeding a regular meal to which a suspension of barium was added after which periodic X ray pictures were taken

## *CURRENT CONCEPTS REGARDING ETIOLOGY OF BENIGN GASTRIC ULCER*

With these experimental studies and clinical observations in mind the question then arose as to the role of the pyloric antrum in the etiology of benign gastric ulcer (19) As previously mentioned gastric ulcers have not infrequently developed following pyloric stenosis produced by the healing of a duodenal ulcer These clinical observations were clearly shown by Huber and Huntington (11) However since the majority of benign gastric ulcers were not associated with organic pyloric stenosis the role of stasis from atony of the gastric musculature which is equally effective in producing a hypersecretion of gastric juice of antral origin was then studied in patients with gastric ulcer

### MEASUREMENT OF GASTRIC EMPTYING BY MOTOR MEAL

In attempting to determine whether stasis exists in patients with benign gastric ulcer the use of a new motor test meal was studied The meal

Gastroduodenostomy

Alternate method of anastomosis

Fig. 14.—Transplantation of the antrum of the stomach into the side of the colon as a diverticulum and reconstruction by end to end gastrojejunostomy

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Fig. 15.—Jejunal ulcer near gastroenterostomy. The antrum of the stomach had been transplanted into the colon twenty two days earlier

twelve hour nocturnal secretion one is impressed that the average output of free HCl in the gastric ulcer patient is approximately half the amount secreted by the normal individual suggesting hypofunction of the secretory fibers in the vagus nerves. It is known that in patients with duodenal ulcer there exists both hypersecretion and hypermotility of the stomach. Therefore the depressed twelve hour night secretion of vagus origin seen in patients with gastric ulcer suggests a concomitant hypomotility as a result of hypofunction of the vagus nerves. Evidence cited confirms the delayed gastric emptying time present in most patients with benign gastric ulcer.



Fig 17.—Patient L. B.'s benign gastric ulcer showing retention of barium meal in stomach. *Left* two hours after ingestion; *right* twelve hours after ingestion.

The summary of a patient with a typical benign gastric ulcer is presented below.

**Case History L. B.** This 56 year-old male entered the hospital with a two year history of postprandial gas pains in the upper abdomen. This distress became worse during the past three to four months and was frequently accompanied by vomiting. He had lost thirty pounds since the onset of his symptoms. X rays revealed a large ulcer crater on the lesser curvature in the midportion of the body of the stomach. There was no evidence of deformity or obstruction at the pylorus to suggest previous duodenal ulcer disease. Two twelve hour night secretion studies yielded 0 and 8 mEq respectively. A motor test meal showed approximately 50 per cent retention of barium in the stomach eleven hours following ingestion (Fig 17). During this entire period hourly samples of gastric content showed considerable free acid ranging from 13 to 73 clinical units. Gastroscopy revealed the large benign appearing ulcer and exfoliative cytology showed no malignant cells. A subtotal gastrectomy was done with uneventful postoperative recovery. The ulcer proved benign histologically.

consisted of meat eggs milk toast and cereal mixed with barium sulfate Following the ingestion of this meal samples of gastric content were secured at hourly intervals over long periods of time and the concentration of free HCl determined X ray examinations were made at intervals following the meal until the stomach was empty To date the majority of patients with benign gastric ulcer without mechanical obstruction at the pylorus have shown significantly lengthy emptying times ranging from eight to fifteen hours after the ingestion of the test meal Similar studies



FIG 16 —Stenosis of the pylorus with retention of food in antrum as a result of a high lying gastroenterostomy *right*

in normal subjects revealed emptying times ranging from three to six hours Secretory studies showed a marked response in acid secretion which persisted as long as the stomach contained food As a result of these motility studies we can assume that stasis does exist in patients with benign gastric ulcer Whether this stasis or gastric retention existed prior to the development of the ulcer or resulted from the edema and inflammatory reaction along the lesser curvature about the lesion has not been shown to date

However there has been some evidence from clinical studies of patients with gastric ulcer suggesting that stasis as a result of gastric atony may exist prior to the formation of a lesion If one recalls the values of the

H N The effect of vagotomy of the main stomach on Heidenhain pouch secretion S Forum 1952 Philadelphia W B Saunders Co 1953
6 SMITH C A MOULDER P V and ADAMS W E Gastric ulcer following esophagogastric anastomosis for carcinoma of the esophagus or gastric cardia Ann Surg Vol 146 No 4 October 1957
7 RIGLER S P OBERHELMAN H A JR BRASHER P H LANDOR J H and DRAGSTEDT L R Pyloric stenosis and gastric ulcer Arch Surg 71 191–95 1955
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15 KANAR E A SCHMITZ E J NYHUS L M MOORE H G JR SAUVAGE L R STORER F H and HARKINS H N Effect of high low and medium gastrojejunostomy to the main stomach on Heidenhain pouch secretion Am J Physiol 175 167–69 1953
16 STEVENSON J K JESSEPH J E JONES T W and HARKINS H N Heidenhain pouch secretory response to gastrojejunostomy as affected by position of the stomach and variation in stomal diameter S Forum Vol 7 1956
17 WOODWARD E R EL GEZIRI M F SCHAPIRO H and PLZAK L F The effect of gastroenterostomy on the gastrin mechanism Arch Surg 74 694–98 1957
18 DRAGSTEDT L R OBERHELMAN H A JR and SMITH C A Experimental gastrojejunal ulcers due to antrum hyperfunction Arch Surg 63 298–302 1951
19 ——— A concept of the etiology of gastric and duodenal ulcer Am J Roentgenol 75 219–29 1955

What other clinical observations support the suggestion that a hyper secretion of gastric juice of humoral origin is responsible for gastric ulceration? It is in the response to gastric surgery for duodenal and gastric ulcer that this concept has been strengthened

When gastroenterostomy was widely used in the treatment of peptic ulcer a high incidence of marginal ulceration was encountered following operation for duodenal ulcer but rarely for gastric ulcer These observations are in harmony with the view that gastric ulcers are usually due to a hypersecretion from stasis of food in the stomach and that this stasis is relieved by gastroenterostomy In duodenal ulcer patients the hypersecretion of gastric juice is of nervous origin persists after gastroenterostomy and causes marginal ulceration

Second when only a partial or lower resection was performed for duodenal ulcer patients stomal ulceration was not infrequent but when this procedure was performed for gastric ulcer stomal ulceration rarely occurred Here again it may be suggested that the low resection with removal of the antrum abolishes the cause for the excessive secretion of gastric juice in gastric ulcer patients and permits them to remain well In duodenal ulcer patients the nervous phase of secretion persists after removal of the antrum and as a result a new ulcer develops

Third the good results secured by the Kelling Madlener operation for high lying juxta esophageal gastric ulcer may be explained by this new concept In this procedure a hemigastrectomy or antrectomy leaving the ulcer *in situ* results in healing of the gastric lesion if benign Thus through these clinical studies and observations this concept has arisen gastric ulcer is caused by excessive gastric secretion due to antrum hyper function from stasis of food Further studies are in progress in order to provide further factual information regarding this concept

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5 SCHMITZ E J KANAR E A STORER E H SAUVAGE L R and HARKINS

ing with him have had charge of the radiation treatment of peptic ulcer in collaboration with Walter Palmer and his associates Finally James Williams has gathered for me the manuscripts and illustrations prepared by various members of our staff in recent years

## HISTORICAL

X ray examination of the upper alimentary tract began to be clinically important about fifty years ago receiving added impetus from the work of such pioneer radiologists as Russell D Carman Walter Mills and James Case

In Carman's day fluoroscopy was paramount Such photographs as were made were of secondary importance but by the early twenties the substitution of film for glass plates led several radiologists in Europe to employ them as important adjuncts to fluoroscopy of the upper alimentary tract Until approximately 1935 however except for the work of L G Cole these newer methods received scant attention in the United States Even today though most American radiologists recognize the value of films the general practice is to place major reliance on large films made following fluoroscopy and to look upon the so called spot films made under fluoroscopic control as interesting sometimes helpful but not of major importance Like most European and a few American radiologists we are in complete disagreement with this view and suspect it has developed because of the technical inadequacy of most commercial American filming fluoroscopes All commercial fluoroscopes are equipped with under table grids over table tubestands and full size fluoroscopic screens so that in addition to fluoroscopy they can be employed for almost every type of radiography But this flexibility which is so emphasized by the commercial manufacturers has severe technical disadvantages

Our own instrument is designed to do well a very few types of examinations—in particular the fluoroscopy and filming of the upper alimentary tract bronchography myelography and detail filming of segments of bowel for polyps Of the material that follows non radiologists may prefer to read only the three sections entitled Theory of Examination X ray Findings in Peptic Ulcer" and X ray Treatment of Peptic Ulcer skimming or ignoring completely the three sections entitled Apparatus The Barium Mixture and Routine of Examination

## THEORY OF EXAMINATION

In patients of average and over average build the fluoroscopic image of the upper alimentary tract is extremely faint even when one employs the

J W J Carpender et al Radiation in the Therapy of Peptic Ulcer Am J Roentgenol Vol 75 No 2 1956

PAUL C HODGES

# 5 X-ray Diagnosis and Treatment of Peptic Ulcer

There is general agreement today as to the radiologic criteria which govern the diagnosis of peptic ulcer—those criteria which enable us to distinguish benign ulcer from ulcerating neoplasm and those which are indicative of healing scarring and recurrence Agreement is less complete as to the technical means best suited to satisfying these criteria Since our technical facilities differ from those commonly used in this country I shall devote most of my space to these facilities and the way in which we employ them

It might be better for me to mention none of my associates by name lest failure to mention some imply failure to recognize the importance of their contributions All of them have contributed ideas and developed technics all have taken an active part in the daily clinical work but a few have made other types of contributions as well Fred Templeton was the first to organize our thinking in the matter of peptic ulcer with his book *The X ray Examination of the Stomach* [1] which still serves as basic instruction for our student radiologists Russell Morgan s phototimer has had one of its most practical applications in our filming flouroscope Three radiologists in succession—Russell Nichols Sidney Nelson and Robert Moseley—have continued the collection of material that was started by Fred Templeton and have assumed the prime responsibility for improving technics and transmitting information and skills to succeeding groups of students J W J Carpender and the radiation therapists and physicists work

[1] F E Templeton *X ray Examination of the Stomach* (Chicago University of Chicago Press 1944)

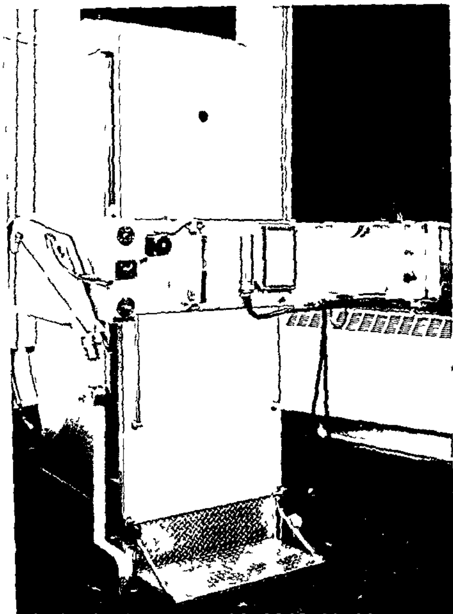


Fig. 1.—The filming fluoroscope in the vertical position with gate pulled forward *completely and step in lowest position*

most sensitive screen available and works at 90 kv and 3 ma. The observer fluoroscoping in a room illuminated sufficiently well for the reading of newsprint cannot see the fluoroscopic image at all. Even when all light is excluded save that from the screen he is barely conscious of the image until his eyes are dark accommodated, a physiological process requiring not less than fifteen minutes. In the dark accommodated eye it is the rods rather than the cones that do the seeing and, of course, rod vision is insensitive to fine detail. Increasing the intensity of the X-ray beam increases the brilliance of the image but tube life and particularly the welfare of both patient and examiner preclude fluoroscopy at voltages and currents significantly greater than those employed by us. A decade ago it seemed probable that electronic amplification of the fluoroscopic image would eliminate this difficulty but the hope has been realized only to a limited degree; for the moment at least, almost all fluoroscopy of the upper alimentary tract is done without amplifiers.

In spite of these inherent limitations an experienced and skilful examiner does an astonishingly good job of detecting fluoroscopically even very small and very shallow ulcer craters. He does even better when he works with a filming fluoroscope combining filming with fluoroscopy. In most cases films merely provide objective evidence of lesions that are described in the fluoroscopic notes; sometimes they demonstrate normal mucosa where the fluoroscopist suspected a lesion and occasionally they suggest the presence of a lesion where none was suspected, thus providing an indication for repeating the examination. Ideally the radiologist fluoroscopes and then films every square inch of the mucosa of the upper alimentary tract, but even in young, slender, healthy subjects the ideal is seldom attained and in short, fat, old, infirm patients one must be content with gross departure from the ideal. As in so many other phases of medicine, positive findings are reasonably dependable but negative findings by no means rule out the possibility that lesions are present.

## APPARATUS

Our filming fluoroscope (Fig. 1) has been under development for nearly a quarter of a century but its two most important features long ago reached approximately their present day form, namely, the use of a very small fluoroscopic screen and the employment of 7 × 17 films with four frames or spots on each. To provide rigidity and facilitate compression during certain phases of the work, the screen and film moving mechanism is supported at both sides of the table rather than merely at the rear. This assembly (Fig. 2) hinges upward as patients enter or leave (Fig. 3); hence we refer to it as the gate. In earlier models we suspended a conventional large fluoroscopic screen from the hinge when the gate was

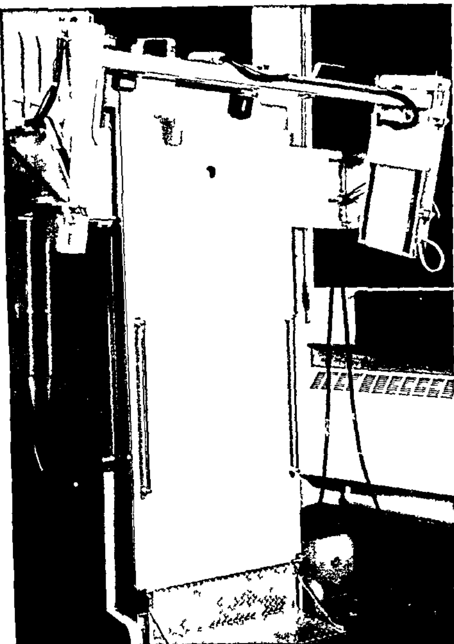


Fig 3 —Most examinations begin and end with instrument in vertical position and gate hinged upward On posterior surface of gate *left* the film carriage motor *right* balsa wood compression block at rear of right hand support latch for retaining gate in "up" position and beneath it rubber-covered loop of chain used as handle to facilitate upward hinging of gate Handrails at either side of table provide support for feeble or apprehensive patients

folded up and we began the examination with the large screen employing the small one merely for fluoroscopic positioning of parts preliminary to filming All of us soon found however that it was preferable to do the entire examination with the small screen After the large screen had hung on the wall gathering dust for several years we retired it to the shop and made no provision for it in subsequent models of the fluoroscope

SIGNIFICANCE OF SMALL SCREEN

If one is willing to accept a small 4¼ × 7 screen as the only one on his filming fluoroscope he reaps two important rewards at the cost of one misconception The latter is the spurious belief that one cannot con

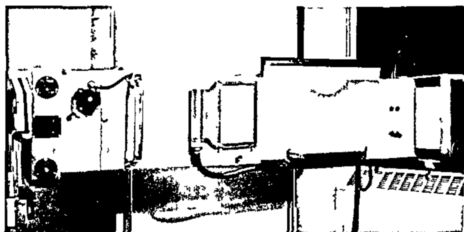


Fig 2—Cart of filming fluoroscope completely pushed in toward table top Film cassette partially inserted in carriage Details in text

duct adequate fluoroscopy of the abdomen and thorax without a large screen and the rewards are *simplicity in design and operation* which result in improved quality of fluoroscopic and film image and above everything else reduction in tissue dose to the patient and to the operator

This matter of the clinical adequacy of a small screen is not unlike the situation in microscopy Even under low power the total amount of tissue that can be seen at one time is small *but the experienced microscopist* moving the slide about beneath the objective becomes oblivious to the limitation in field size and thinks of the section as a whole The same is true in fluoroscopy No matter how large the screen may be one is able to fix his attention on only a small part of it at any one time In using a well designed fluoroscope he moves tube and screen about quickly and easily becoming unaware of the fact that he is examining the field piece meal New radiologists on joining our staff are at first dismayed by the

of the X ray tube as the gate is moved forward through 12½ to its maximum distance from the table top Stop 2 moves forward a distance of 4½

**Stop 3** measures 2¾ × 4½ and is fixed at a point 16 in front of the target

**Stop 4** measures 4¼ × 7 and is the window in the lead armor of the gate

If only Stops 1 3 and 4 were employed collimation would be fully adequate only when the gate was at the limit of its travel away from the table top For shorter distances the beam entering the patient would be larger than necessary with consequent increased dose to patient and examiner and deterioration of image quality However the geometry of the travel of Stop 2 is such that when it is added to the system the rectangular beam entering the patient is barely large enough to fill the area of Stop 4 for all positions of the gate

COMPRESSION LOCK

Mounted on the shaft that ties together the counterweights and drives Stop 2 is a drumlike assembly similar to the coaster brake of a bicycle When this drum is clamped by a stationary external brake band it is possible to rotate the shaft within the drum in the direction corresponding to movement of the gate toward the table top but not in the opposite direction The compression lock is an eccentric which operates the brake band When the lock is off the shaft together with its drum rotates freely in either direction when it is on the drum is immobilized and the shaft is able to rotate only within the drum and only in the direction that allows the gate to move inward

PHOTOTIMER

In the center of the left hand support column (see Fig 2) is a four station selector switch for selecting any one of four phototimer settings

**Station I** is calibrated for gastric and colon examinations and for frontal myelograms on adults

**Station II** is calibrated for esophagus examinations and for bronchograms on adults

**Station III** is used for lateral myelograms on adults

**Station IV** is used for examinations of all sorts on babies and small children

The screen phototube assembly shown in Figure 2 has been described elsewhere [3] It is completely light tight and includes a lightweight pipe of ¼ in lucite carrying on both anterior and posterior surfaces 4¼ × 7 sheets of DuPont No 564 screen Except for the small area directed at the photocathode of the XP21 tube it is completely coated with aluminum deposited by evaporation in vacuum

[3] Paul C Hodges Photoelectric Timing in General Radiography *Acta radiol* Supp 116 (Seventh International Congress of Radiology)

Spartan simplicity of our instrument its screen seems hopelessly inadequate for fluoroscopy of the chest and abdomen its film frames far too small But as these workers become accustomed to our instrument they find that a small screen and small film frames are not actually disadvantageous and they wonder how they put up with the inconveniences of commercial filming fluoroscopes

THE GATE

This is a 12 × 48 × 2 mechanism which contains a reciprocating grid and the film carriage it holds the screen phototube assembly operating handles four electrical switches a pilot light on its front surface (Fig 2) and a balsa wood compression block on its rear surface (Fig 3) The rear surface is covered by a continuous sheet of 1 mm magnesium in front of which is a sheet of lead 1 mm thick pierced by a 4½ × 7 window behind the fluoroscopic screen Above below and for 2 in on either side of this window the sheet of lead is reinforced by an additional ¼ mm of lead

A Liebel Flarsheim 7 × 7¾ medium focus 80 line moving grid is mounted in front of the window It is stationary for fluoroscopy but oscillates as films are being made with an amplitude of 1 in and a rate of one stroke per second Earlier models employed stationary linear or cross hatched grids and many of the films used in Figures 8–30 were made with them rather than with a moving grid

COLLIMATION OF X RAY BEAM

The gate may be pushed to within 8½ in of the table top or moved out 21 in from the top a total of 12½ in of travel Two sprocket chains connecting the gate to its counterweights operate a shaft on the tube carriage which performs three important functions (1) It ties together the right and left hand counterweights forcing the two ends of the gate to move in unison (2) It provides a simple mechanism for compression presently to be described (3) Through a gear train it drives a rectangular lead diaphragm mounted in the lead lined base to which the X ray tube is attached This diaphragm is pierced by a 1½ × 2⅝ rectangular opening known as **Stop 2** which is one of four that collimate the X ray beam to minimize the dose to patient and examiner and improve the quality of the fluoroscopic image

**Stop 1** measuring ⅝ × [illegible] is fixed at a point 2[illegible] in front of the target of the X ray tube

**Stop 2** measuring 1[illegible] × 2[illegible] is the moving stop mentioned above With the gate as near as possible to the table top Stop 2 lies 9[illegible] in front of the target

then depressed the carriage motor is energized, solenoid-operated pin No 1 rises in the carriage track and the film carriage moves rapidly from its zero position to the left stopping with its first film frame centered at the window After the carriage has been arrested by pin No 1 it is held there by the motor which is stalled but still in circuit and still pulling

When the foot switch has been closed to make the exposure and then released after the exposure has been completed, the motor reverses re

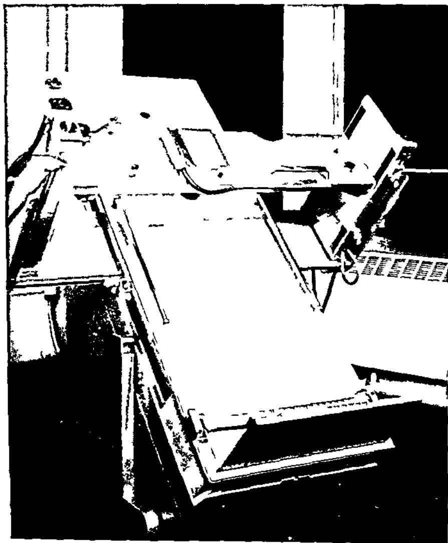


Fig 4 —Fluoroscope tilted 45 toward horizontal

A Patterson B2 fluoroscopic screen is mounted in front of the detector screens and behind a sheet of standard quality lead glass Below the screen is a push button switch labeled "shift" which operates the change over mechanism bringing the film into position for exposing

The push button switch located at the top of the handle at the left side of the gate and labeled "bias" puts phototimer station II in circuit regardless of the position of the phototimer selector switch Experience shows that if the examiner turns the dial to station II for making films of the esophagus during the course of a routine gastric examination he is apt to forget to return it to station I after the esophagus films have been made Since the bias switch operates only while the operator's thumb is on the push button the phototimer returns automatically to station I as soon as the push is released

At the top of the left hand support column above the selector switch is a push switch labeled "FL Timer Ext 60 sec" When during the progress of fluoroscopy the limit timer on the control stand (see Fig 6) shuts off the operator may obtain an additional one minute of fluoroscopic time by pushing this switch which energizes a thermal relay paralleling the five minute timer

TILTING MECHANISM

The left hand support column also holds the switch for tilting the fluoroscope (Fig 4) Tilting is done by 110 volt single cycle a c motor connected to the table through a friction clutch and a worm drive When the switch is in the central position power is off With the switch in the upward position the table tilts toward the horizontal at a rate of 90° in ten seconds when the switch is thrown downward direction of tilt is reversed and the table is brought to the vertical position Regardless of the direction of travel when the switch is returned to the central position and a c power is disconnected d c from a dry rectifier power pack is supplied to the motor windings for a fraction of a second providing a dynamic brake to prevent coasting

FILM TRANSPORT

At the right side of the gate there is a small green pilot light that goes on when the carriage has returned to zero after the fourth exposure To the left of it is a fuse for the circuits in the gate Near the lower right hand corner of the gate there is a five position indexing switch which advances automatically clockwise as exposures are made and is reset manually With the indexing switch at its extreme counterclockwise position the machine is ready for the first exposure and a luminescent disc illuminates a single drill hole in the cover of the gate When the shift push button is

then depressed the carriage motor is energized solenoid operated pin No 1 rises in the carriage track and the film carriage moves rapidly from its zero position to the left stopping with its first film frame centered at the window After the carriage has been arrested by pin No 1 it is held there by the motor which is stalled but still in circuit and still pulling

When the foot switch has been closed to make the exposure and then released after the exposure has been completed the motor reverses re



FIG 4 —Fluoroscope tilted 45 toward horizontal

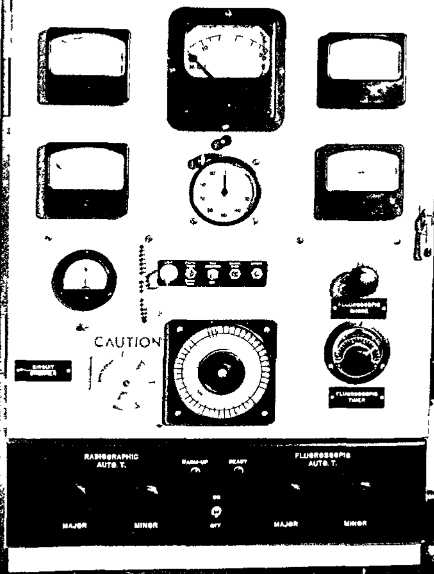



Fig 5 —Control panel with functions of most components indicated by labels Five rectangular meters *Left upper* radiographic kilovoltage *left lower* radiographic milli

turning the carriage to its zero position and advancing the indexing switch one step so that the luminescent disc now illuminates two holes in the front cover at the gate The motor is now stalled again but this time it exerts its pull in the opposite direction and holds the carriage in the zero position

After completion of the fourth exposure the indexing switch moves to the fifth position placing the luminescent disc behind a large hole in the cover lighting the green pilot light and disconnecting the shift push button The operator now removes the exposed film from the carriage substitutes a fresh one and resets the indexing switch manually all of these operations being feasible with the gloved hand

While the film carriage normally returns to its zero position automatically when the foot switch is released it is sometimes desirable to return the carriage without making an exposure for this purpose a push button has been provided at the left side of the gate Above this return push button is the motor for reciprocating the grid

THE X RAY TUBE

We use currently a Machlett Dynamax No 46 with twin 1 5 mm focal spots and an auxiliary blower Fluoroscopy is done at 90 kv and 3 ma with the anode rotor pulsed for two seconds out of every thirty seconds Films are made at 90 kv and 150 ma with the rotor running continuously

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amperage *right upper* fluoroscopic kilovoltage *right lower* fluoroscopic milliamperage *top center* milliampere second meter put in circuit by push button beneath it

*Lower left* round dial valve tube test meter employed at beginning and end of day s work to test intactness of the four valve tubes in the X ray generator Actually this is a d c milliammeter wired in series with the a c milliammeters but normally shunted out by small push button switch located beneath it When all four valves are intact and machine is operated with test meter in circuit needle vibrates about 0 If one or more of the valve tubes is non conducting needle deflects to the right or the left

The round dial in the center is a time recorder employed only for calibration of machine

Small rectangular Bakelite panel below time recorder carries five switches identified as follows from observer s left to right *Switch 1* panel light switch When this switch is closed and motor timer is in circuit panel light burns but goes off automatically when machine is switched to phototimer Ordinarily motor timer is used only for testing but on those rare occasions when one does clinical work with the motor timer he removes cap from switch 1 and turns the panel light off Of course he must remember to turn it on again and replace the cap for normal operation *Switch 2* is the timer selector switch for changing the machine over from motor timer to phototimer *Switch 3* puts the time recorder in circuit for calibrating *Switch 4* is a double pole double throw spring return change-over switch In normal position machine is on fluoroscopy but when switch is held in the "down position machine is on filming setting *Switch 5* push button—exposing switch Except for testing and calibration change over and exposing are accomplished at the fluoroscope by means of a push button and the foot switch

THE FLUOROSCOPE STEP

Such a trivial thing as a poorly designed fluoroscope step can waste the time of the examiner contribute to his fatigue and reduce the validity of his findings In commercial instruments steps can be attached at various distances from the bottom of the fluoroscope but this requires unloading the patient a procedure so laborious that it seldom is employed Instead the step usually remains at its lowest position and the examiner whether he be short or tall adjusts his eye level to the height of the patient by adjusting the height of his stool Manufacturers who cater to our colleagues the dentists and our profession s ancient rivals the barbers have considered it important to provide those workers with facilities for adjusting their subjects to a convenient working level and we have provided ourselves with the same convenience (Fig 6) The location of the step is controlled by a switch on the right hand support column which operates a hydraulic piston to move the table top and the attached step a maximum distance of 8 in With the switch in the central position table top and step are fixed Moving the switch handle upward energizes the motor of a small pump delivering oil to the bottom and removing it from the top of a hydraulic cylinder Moving the switch handle downward reverses the direction of motor rotation and oil flow driving table top and step downward

Careless doctors and technicians occasionally allow the examiner s stool or other furniture to be pushed into the path of the fluoroscope as it is being tilted up from the horizontal position with resulting damage to stool and fluoroscope and alarm if not injury to the patient If our instrument is tilted in this careless manner no harm results because as the step makes contact with the stool it angles forward a few degrees releasing a normally open microswitch at the lower end of the table top and disconnecting power from the tilting motor

Eight inches of step travel is adequate for all but the shortest adults for them and small children a wooden stool is placed on top of the hydraulically driven metal step

## THE BARIUM MIXTURE

It is more than forty years since barium sulfate replaced insoluble bismuth salts for the opacification of the alimentary tract but even today there is no uniformly accepted formula for barium mixtures Some have urged that the best mixture is barium sulfate and water but there are serious practical objections to this with few advantages Commercial vendors offer a great variety of brands and proclaim the merits of this or that combination of vehicle flavoring coloring and perfuming but a single American

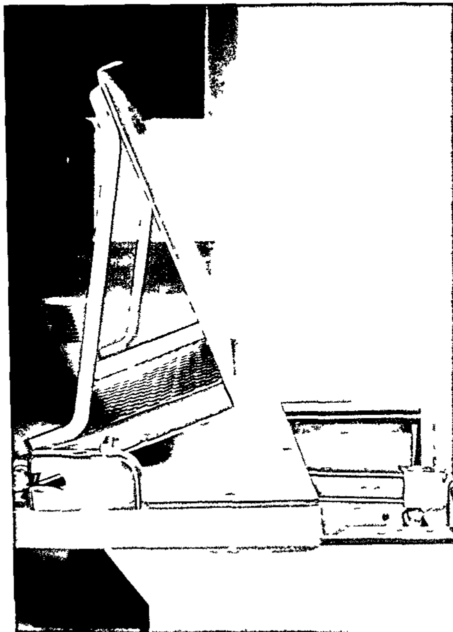


Fig 6 —The fluoroscope step with table raised to upper limit of travel by the hydraulic piston *right* Step has been tilted forward to expose microswitch at lower edge of table top and relationship between notched block heavy support pin and lighter retaining pin

manufacturing chemist produces almost all the barium sulfate used in the United States and most compounders of mixtures buy their barium from this source Advertising claims for special processing adjustment of grain size control of surface tension and so on have little or no basis in fact In straining for distinctive flavor and aroma gross overflavoring sometimes results and most patients are resigned to the belief that distastefulness is an unavoidable attribute of all barium mixtures We compound our own barium mixture and with few exceptions our patients find the drink actually palatable

Our manufacturing pharmacy buys U S P barium sulfate in 250 pound drums and as a flavoring and suspending medium employs a small amount of a dry cocoa mixture sold by the Nestle Company under the brand name Quick (Dutch process cocoa sugar lecithin as an emulsifier vanillin and other flavoring) Barium sulfate 90 per cent by weight is mixed with Quick 10 per cent by weight and four pound lots of this dry mixture are put up in paper bags Added to three quarts of water the contents of one bag makes enough barium mixture for ten patients Our dispensing mixer (Fig 7) produced in our experimental shop consists of a variable speed stirring blade and a stainless steel pot with a dispensing valve in the bottom Without the aid of tools it may be completely disassembled for its daily cleaning and sterilizing

A few minutes before work starts each morning the technician measures three quarts of water into the pot dumps into it a four pound bag of the dry barium mixture and starts the stirring blade at high speed reducing it to low after a few minutes

Instead of the glass mugs that formerly took up much space and required much dishwashing we now use disposable paper cups in stainless steel holders and flexible paper drinking tubes have supplanted tubes of glass or aluminum For the initial mouthful of barium the technician measures 30 cc of the mixture into a paper cup and when this has been drained by the patient she fills the cup to within approximately ¹ in of its top the amount being something more than 250 cc After ten patients have been examined she discards any balance remaining in the pot adds three more quarts of water and another bag of barium mixture and within a few minutes in the dark and without interrupting the flow of her other work or that of the radiologist she is ready to proceed with the next ten patients

At the start of each day s work the technician makes up about 250 cc of barium consisting of three parts of the barium mixture and one part of water for the occasional case in which the examiner calls for thick barium" for special examinations of the esophagus

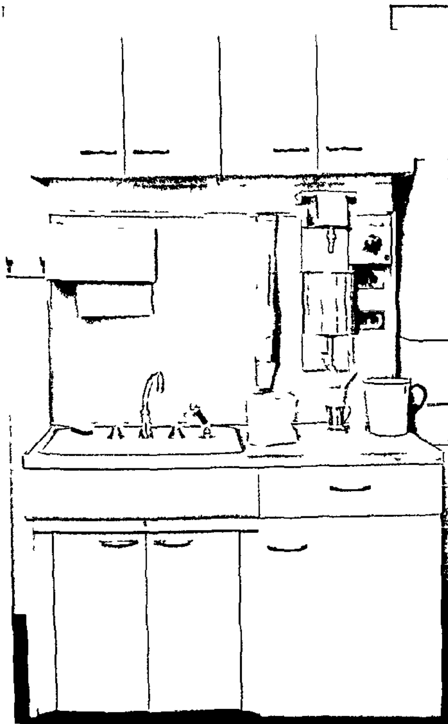


FIG 7 —The barium suspension apparatus *On the work surface left to right* four pound bag of dry barium-cocoa mixture paper cup in metal holder one-ounce measuring glass and two-quart enamel steel measuring pitcher *Attached to back panel* paper [dispenser] and motor-driven barium mixer

These arrangements simple as they are are important time savers for technicians working in the dark and responsible for many other details which do not lend themselves to mechanical simplification

## ROUTINE OF EXAMINATION

Our student radiologists are required to follow a stereotyped routine until they have convinced us that it is safe to allow them to improvise but our more experienced examiners employ innumerable variations even for normal patients and all of us vary routine to meet special problems as they arise The general plan is to begin with a small amount of barium and with the aid of gravity and the palpating hand employ it alternately to coat and fill various segments of the gastric mucosa fluoroscoping and filming as we go Following this the full 250 cc of barium mixture is ingested and the closing phases are concerned with the bulb and the second portion of the duodenum Rarely do we make less than eight frames or individual exposures twelve is perhaps the most common number and occasionally there may be sixteen twenty or even twenty four

The patient scheduled for X ray examination of the upper alimentary tract abstains from food or liquids after midnight and presents himself at eight the following morning As he stands with his back against the table top and facing the screen and the examiner a rapid survey is made of thorax and abdomen if this is negative he takes 30 cc of barium mixture into his mouth and swallows it when so instructed The examiner watches the bolus pass through the esophagus into the stomach and then with the lead rubber gloved hand he manipulates the abdomen to smear barium over the gastric mucosa and mix it with any fluid that may have been in the stomach Usually the antrum and bulb are not examined in detail at this time but it is well to identify them Occasionally a bulb that fills readily early in the examination will be recalcitrant later

Now the patient is turned into the lateral position his right side against the table top After the table has been tilted to the horizontal he rolls onto his back The purpose of this maneuver is to coat the mucosa of the distal half of the stomach with barium first and then to trap air in that portion It is well to proceed rapidly with filming before gastric secretion dilutes the barium that has been deposited on the mucosa

The patient now takes the drinking tube into his mouth and on signal from the examiner swallows three mouthfuls while films are being made of the esophagus and the fundus With the patient first on his back then in the full prone and prone oblique positions the remainder of the barium is ingested and fluoroscopy and filming of the esophagus stomach and bulb are continued Finally the patient is tilted to the erect position so that air will balloon the fundus and barium will fill the body antrum and

bulb with a gravity level at the boundary between air and barium The examiner now carefully examines every portion of the stomach and bulb palpating deeply with his gloved hand with gauze covered cotton pads or with the balsa wood compression block It is now that the antrum bulb and second portion of duodenum are usually most easily seen and filmed with and without compression Figure 8 shows twelve frames of a normal stomach and bulb Figure 9 three frames of a normal bulb

## X RAY FINDINGS IN PEPTIC ULCER

### ESOPHAGEAL ULCER

Carcinoma diverticulum varices chemical stricture foreign bodies and cardiospasm are the conditions for which most X ray examinations of the esophagus are done Peptic ulcers are seen only rarely The case illustrated in Figure 10 is that of a 58 year old woman who had a duodenal ulcer with pyloric obstruction so severe as to require gastroenterostomy As a result of frequent attacks of vomiting a peptic esophagitis had developed and this caused severe esophageal stricture Eventually a small ulcer crater developed in the stenosed segment of the esophagus

Palpation and compression so useful in gastric and duodenal ulcer are impossible in the esophagus rotation gravity persistence and above everything else luck are the radiologist s only recourses

### GASTRIC ULCER

For approximately twenty years the X ray examination completely overshadowed all other diagnostic methods for detecting ulceration of the gastric mucosa and for differentiating between benign ulcers and ulceration in gastric neoplasms For another twenty years it shared these responsibilities with gastroscopy more recently in the matter of differentiation exfoliative cytology has joined the team Proponents of each of these three methods understandably have gone to considerable effort to weigh the relative dependability of each but carried too far this induces rivalry and introduces guessing and playing the percentages When little other than X ray was available the radiologist was morally bound to push to the utmost his efforts to establish not only the existence but also the exact nature of gastric lesions but today he serves best when he leaves to gastroscopy and cytology those judgments that they are able to render with relative ease and dependability and concentrates on judgments which are easier for him than for them

Theoretically X ray differentiation between benign peptic ulcer and ulcerating gastric neoplasm is a simple matter but in practice it frequently is difficult and sometimes impossible In theory the crater of a benign peptic ulcer is spherical or tongue shaped protrudes beyond the serosa

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Fig 9 —Normal duodenal bulb A normal bulb filled view The skill and diligence of the examiner are important in obtaining good films of the bulb but with anatomy as favorable as this case the making of good films is easy Even here however one cannot be sure of the absence of a crater until a compression view is made (see Fig 26)

*B* compression view (not the same patient as in *A*) Normal mucosa no crater or obstruction C air view (still another case) The duodenal bulb usually such a definite entity to the radiologist is much less real to the surgeon and pathologist and sometimes lacks even radiologic existence Its base is a genuine anatomical structure namely the intestinal side of the pyloric muscle but its apex so obvious in these three X ray views lacks an anatomical counterpart Occasionally the radiologist sees the barium filled bulb only momentarily a fleeting phase of gastric emptying and sometimes he must be content with air views such as this one

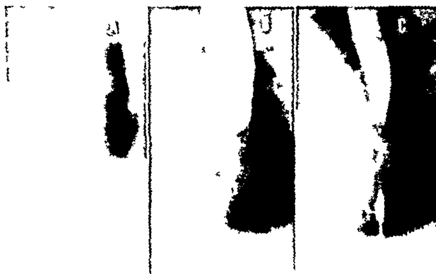


Fig 10 —Esophageal ulcer in peptic esophagitis *A* severe stenosis lower third of esophagus following vomiting due to stenosing duodenal ulcer *B* and C six months later 1 × 2 mm ulcer crater in stenosed segment

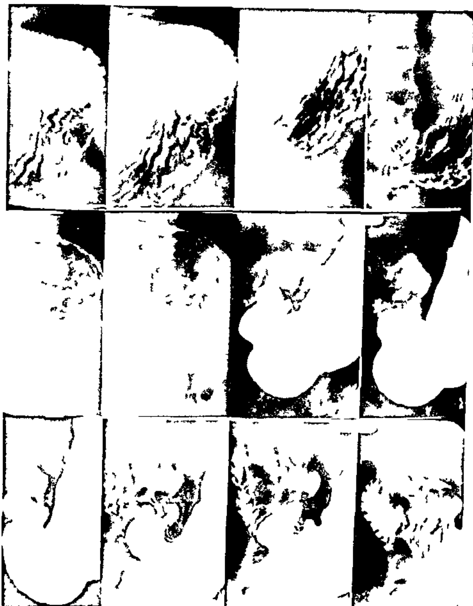


FIG. 8.—Normal stomach and duodenal bulb. *Top row*, body and antrum seen in so-called "mucosal relief" by virtue of barium smeared mucosa contrasting with trapped air; fundus and esophagus. [illegible] filled views.

*Second row*, patient standing. Body, antrum and bulb are filled; air billows the fundus and there is a gravity level at the junction between barium and air.

*Third row*, employing varying degrees of rotation and compression, antrum, bulb and second portion of duodenum are visualized.

*Small multiple craters*—Multiple discrete small craters are uncommon but when present are almost certainly benign (Fig 12)

*Hour glass deformity*—In the early days of gastric radiology fluoroscopy and radiographs had such limited scope that only gross lesions could be detected One of the most dramatic findings was a deep incisura on the greater curvature opposite a lesser curvature crater Because the incisura divided the stomach into upper and lower portions it was termed "hour glass deformity" (Fig 13) Possibly the condition used to be more com




Fig 12—A three benign craters seen in mucosal relief B same in filled views and C a year later D nine years later the craters have healed

shows little or no infiltration of the base and little or no interruption of the mucosal pattern except within the crater itself. Under antacid management benign craters usually heal and if they recur it is frequently at a new site. When gastric neoplasms ulcerate the craters tend to have irregular shape, are usually withdrawn into the lumen of the stomach and are located in intraluminal masses of tumor tissue. These tumor masses stiffen the gastric wall about the crater and interrupt the mucosal pattern for a




FIG 11 —Small benign gastric ulcer. The craters of gastric ulcers frequently are small and most commonly lie along the lesser curvature of the body of the stomach. This one measures 5 × 10 mm. In *views A* and *B* the patient has been rotated to bring it into profile. In C it is seen *en face*. The radiologist called the lesion benign but the surgeon fearing malignancy did a partial gastrectomy. Histologically the lesion was found to be benign.

variable distance beyond the crater. Of course hyperacidity is unusual in gastric neoplasm but when it is present and when antacid therapy is followed by healing of a crater the recurrence is usually at the original site. But inflammatory reaction about a benign crater may produce an X-ray appearance indistinguishable from neoplastic infiltration and very small neoplasms may ulcerate leaving only microscopic residua of tumor.

*Small solitary crater*.—When an ulcer is small and solitary, protrudes beyond the serosa and has normal appearing mucosa about it the X-ray diagnosis is "benign ulcer" and usually this proves to be correct (Fig 11).

internists continue to disagree as to whether benign gastric ulcers ever undergo malignant degeneration, it is recognized by all that small neoplasms may ulcerate so promptly and so completely as to produce a radiographic appearance identical to benign gastric ulcer. Furthermore, a patient with a benign gastric ulcer may have a small neoplasm as well, and there seems to be statistical proof that patients with chronic gastric ulcers are prone to develop gastric neoplasm. In the case illustrated in Figure




Fig. 14.—Healing of a benign peptic ulcer. View *A*, 1.5 × 3.5 cm. ulcer crater on the lesser curvature. *B*, one month after irradiation and antacid therapy, the crater is much smaller. *C*, five months after the first examination, the crater has healed but there is persistence of mucosal scar.

15, a large benign-appearing crater protruded from the lesser curvature of the stomach just proximal to the incisura angularis. Two months later it had healed completely, but meanwhile exfoliative cytology had become positive. Therefore, a few days after the making of view *B*, a subtotal gastrectomy was done. The pathologist reported superficial carcinoma in the region of a chronic gastric ulcer.

*Neoplasm developing in old ulcer site.*—In the case illustrated in Figure 16, a 47-year-old male developed a shallow 1 cm. ulcer crater on the lesser curvature side of the body of the stomach, which healed under management. Seven years later a 2.5 × 3.5 cm. ulcer crater was found at almost exactly the same site on the lesser curvature of the body, and there

mon when acute ulcers were apt to go undiagnosed and untreated until symptoms of obstruction brought them to light Certainly the finding is a rarity today

*Healing as an indication of benignancy*—The ulcer crater that heals promptly under antacid therapy is not invariably but usually benign At the first examination of the case illustrated in Figure 14 the crater on




Fig 13—Gastric ulcer producing hourglass deformity View *A* 3 × 6-mm ulcer crater at lesser curvature of the stomach in a woman giving a one year history of melena and cramping abdominal pain *B* four months after institution of medical treatment the crater has healed but deformity persists

the lesser curvature of the body of the stomach measured 3.5 cm in diameter and 1.5 cm in depth and there was more than a little reason to fear neoplastic infiltration of the gastric wall about it However the patient was given a trial of antacid therapy and within one month the crater was greatly reduced in size and mucosal folds passed directly into it indicating that the infiltration had been inflammatory rather than neoplastic Five months after the first examination healing was complete leaving merely a puckered scar at the lesser curvature

*Healing as a misleading factor in malignancy*—While surgeons and




Fig 16 —Neoplasm developing in old ulcer site *A* benign appearing crater which under management healed View *B* seven years later a huge 2 5 × 3 5 cm malignant looking crater lies retracted into the lumen of the stomach at the old ulcer site *C* one month after *B* and following irradiation of fundus the crater has healed leaving a puckered scar (Subtotal resection one month later again showed neoplasm )

A

B

Fig 17 —A huge benign peptic ulcer The crater measures 8 cm in diameter and has a halo at its base interpreted by us as neoplasm Subtotal resection showed it to be benign

seemed to be neoplastic infiltration of the wall about it However the referring physician believing the lesion to be benign put the patient on antacid therapy and irradiation of the gastric fundus One month later the crater had healed but with persistence of a puckered scar and in the meantime the exfoliative cytology had become positive At the time of subtotal resection a few days later the surgeon believed he was dealing

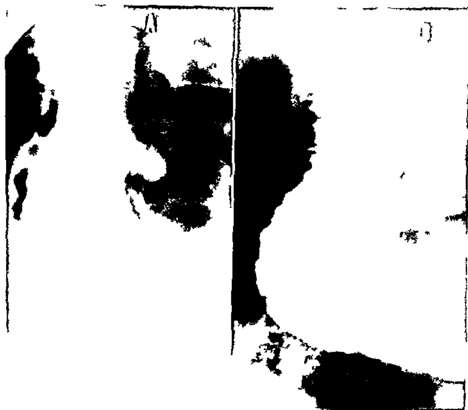



Fig 15 — Malignancy in a healed peptic ulcer View A 1.5 × 1.5 cm ulcer crater protruding beyond the margin of the serosa at the lesser curvature of the stomach B two months later crater has healed but subtotal gastrectomy shows neoplasm

with a benign ulcer and only at microscopy was the malignant nature of the lesion established

*The fact that the crater of an ulcer is large does not prove that it is malignant*—While it is true that most benign ulcer craters are relatively small and that most of the large craters we see represent ulceration in neoplasm large size alone does not justify a diagnosis of malignancy In the case of the 65 year old male illustrated in Figure 17 there had been symptoms for three months An enormous 8 cm ulcer crater was found on




FIG 16—Neoplasm developing in old ulcer site *A* benign appearing crater which under management healed View *B* seven years later a huge 2 5 × 3 5-cm malignant looking crater has retracted into the lumen of the stomach at the old ulcer site *C* one month after *B* and following irradiation of fundus the crater has healed leaving a puckered scar (Subtotal resection one month later again showed neoplasm )

FIG 17—A large benign peptic ulcer The crater measures 8 cm in diameter and has a halo at its base interpreted by us as neoplasm Subtotal resection showed it to be benign



Fig 18 —A benign gastric ulcer that looks malignant A crater 1 5 × 3 cm at lesser curvature of stomach in a 50 year old male At subtotal gastrectomy the lesion was found to be benign

the lesser curvature of the stomach at the incisura angularis It was so large in fact that it was difficult to get it onto our small films We assumed that the condition was ulcerating neoplasm and at operation five days later subtotal resection was done but microscopic examination showed that the lesion was benign

*Failure of ulcer crater to protrude beyond the normal margin of the stomach does not absolutely establish malignancy* —In the case illustrated

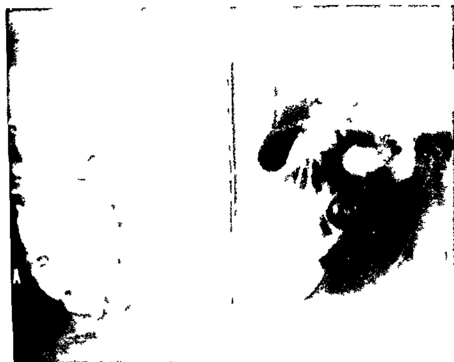



Fig 19 —A benign ulcer crater suspected of being malignant because of location in antrum *A* without compression *B* with compression

in Figure 18 the large 1 5 × 3 cm ulcer crater on the lesser curvature of the body of the stomach fulfils practically all the X ray criteria for malignancy It is withdrawn into the body of the stomach rather than protruding beyond it the surrounding gastric wall is stiff and the mucosal folds do not extend into the crater Not only did the radiologist call it malignant but at the time of operation the surgeon s preoperative and postoperative diagnoses were neoplasm Only when the tissue was examined was the benign nature of the lesion established

*Ulcers located within the pyloric antrum frequently but not invariably are malignant* —In the case illustrated in Figure 19 a 50 year old woman

was found to have a 1.5 × 2 cm ulcer crater in the pyloric antrum The X-ray findings were compatible with benignancy but malignancy is so common in the antrum that the radiologist was not willing to call the lesion certainly benign Partial resection was done the following day and microscopy established the benign nature of the lesion

*Location on greater curvature not a dependable criterion of malignancy* —It is true that most benign gastric ulcers occur on the lesser curvature

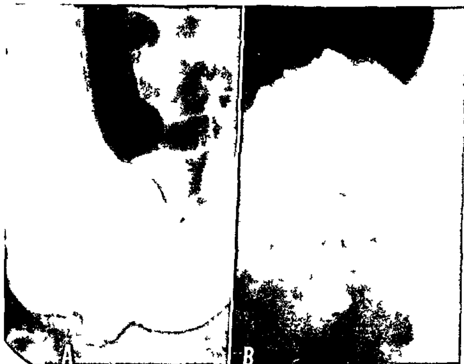



Fig 20—A benign crater on greater curvature of stomach *A* filled view showing 1.5 × 2 cm crater *B* compression views mucosal folds extend without obstruction into the crater

of the stomach and that it is not particularly uncommon to find ulcerating neoplasms on the greater curvature but only by false logic does this lead to the conclusion that any ulcer crater encountered on the greater curvature by virtue of that fact is malignant In the case illustrated in Figure 20 a 1.5 × 2 cm ulcer crater projected straight downward from the horizontal portion of the greater curvature of the body of the stomach with mucosal folds projecting directly into it and without any evidence whatever of a collar of neoplasm or even inflammatory tissue about the neck

One of our junior radiologists miscalled the lesion malignant presum

ably because of its greater curvature location perhaps for this reason at the time of operation a week later the preoperative diagnosis was malignant gastric ulcer A subtotal gastrectomy was done and at gross and microscopic examination of the tissue no neoplasm was found

*Ulcer crater simulating diverticulum* —It is not often that the crater of a gastric ulcer *is* difficult to differentiate from a diverticulum but the difficulty does occur In the case illustrated in Figure 21 diagnosis would not have been easy if the only examination had been that of view *B* This 58 year old male had no demonstrable lesion in the fundus or along the lesser curvature of the stomach at the time of the first examination when view *A* was made A month later he had developed a small ulcer crater high up on the lesser curvature over a period of six months during which numerous examinations were done the lesion grew larger View *B* was approximately eight months after view *A* and the enormous 2 5 × 3 cm crater looked far more like a diverticulum than an ulcer crater X ray therapy was added to antacid treatment and the crater diminished rapidly in size when view *C* was made two months after view *B* it had disappeared completely Of course a lesion which develops and then disappears can not be a diverticulum View *D* shows a genuine diverticulum in another patient Note how closely it resembles the ulcer crater of *B*

*Gastric diverticulum* —Surprisingly enough it is easy to overlook a diverticulum at the fundus of the stomach even when it is large In the case illustrated in Figure 22 a 2 5 × 3 cm diverticulum at the lesser curvature of the fundus close to the lower end of the esophagus was first suspected and then dismissed by the fluoroscopist at the first reading of the film shown in view *A* Another examiner detected it however and arranged for additional raying four days later View *B* shows the diverticulum retaining some of the barium administered four days earlier view *C* shows it filled with new barium and well visualized because the patient has been rotated to bring it into profile Gastric diverticula seldom produce symptoms or require treatment but of course it is embarrassing to overlook them

*Retention of barium in gastric diverticulum* —In the case illustrated in Figure 23 an enormous diverticulum overlooked at gastric examination was detected because it still contained barium at the colon examination on the following day View *A* shows a 3 × 5-cm egg shaped mass containing food and barium which was seen in one of the colon films Following this lead the gastric examination was repeated View *B* shows a huge 5 × 8 cm diverticulum extending directly posterior from the gastric fundus at the point where the esophagus enters It was not filled when the patient was in the standing position when the patient was recumbent the diverticulum was filled but it was obscured by the fundus

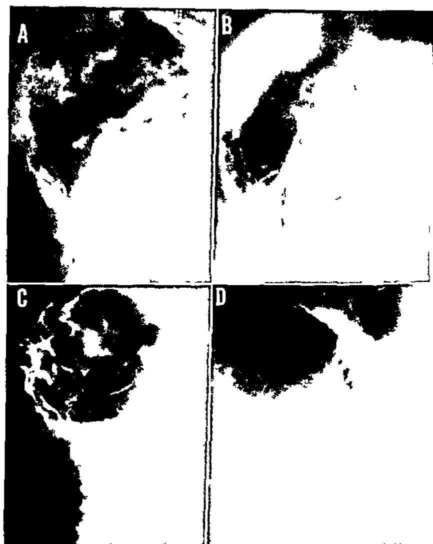



Fig 21 —Ulcer crater simulating diverticulum *A* normal fundus and body of stomach *B* same region eight months later a 2.5 × 3 cm ulcer crater has appeared View *C* two months after *B* crater has healed completely *D* another patient with a genuine diverticulum in the same region




Fig 22 — A a genuine gastric diverticulum near esophageal orifice partially masked by overlying parts of fundus *B* four days later with patient erect retained barium in the diverticulum assumes a gravity level *C* diverticulum filled with new barium




Fig 23 — A view from colon film showing barium retained in huge gastric diverticulum twenty four hours after gastric examination *B* eighteen days later enormous diverticulum that fills only with patient recumbent and is seen only as he is turned into lateral position

it showed up only as the patient was rotated into the full lateral position This illustrates the importance of turning the patient into various positions

DUODENAL ULCER

In more than half the patients submitting to X ray examination of the upper alimentary tract the normal duodenal bulb fills readily with the barium mixture and retains it long enough for adequate filming but sometimes the filled phase is very brief and occasionally there is no differentiation at all between the bulb and the second portion of the duodenum In a typical normal X ray (see Fig 9 A) the distal surface of the pyloric muscle produces a clean cut horizontal base to the bulb and the downward turn where the superior and descending portions of the duodenum meet forms a sharply rounded apex The long axis from base to apex may parallel the spine or be angled toward or away from it and the bulb may lie beneath the ribs where it is inaccessible to palpation or well down in the abdomen where palpation is easy In the erect patient the best view is usually obtained in the first oblique position where the patient's right side is rotated slightly toward the screen but sometimes the reversed or second oblique position is better and occasionally the bulb is thrown free from neighboring structures only in the full lateral position

For many years the X ray diagnosis of duodenal ulcer rested on the demonstration of deformity irritability and obstruction but since the publications of such workers as the late Ake Akerlund the direct visualization of the crater has become the principal aim of the examiner[4] In a severely deformed bulb peripheral scar pockets may simulate craters particularly to the inexperienced examiner on the other hand a frank crater in an undeformed bulb may escape detection if compression is not employed (see Fig 26 B) The mere inability to obtain films of the filled bulb is no longer interpreted as evidence of ulcer deformity deformity of a characteristic type must be seen When deformity produces severe obstruction that fact is obvious to the radiologist but judgments as to the degree of incomplete obstruction should be rendered and accepted cautiously

*Duodenal ulcer with crater in deformed bulb* —The case illustrated in Figure 24 is that of a 32 year old male With the patient in the second oblique position (*A*) an enormous ulcer crater *is seen projecting from the* posterior wall of the seemingly undeformed bulb When he is turned into the first oblique position and pressure is applied (*B*) the crater is seen

[4] Åke Åkerlund The Roentgen Diagnosis of Ulcus Duodeni with Respect to the Local Direct Roentgen Symptoms *Acta radiol* 2 14–27 1923

*en face* with moderate deformity of the bulb about it Three years later (*C*) following healing by medical management the compressed bulb shows only residual ulcer deformity at the apex

*Ulcer deformity of bulb* —Some ulcer craters heal without demonstrable residual deformity but in most cases they leave a puckered scar which may be so pronounced as to be visible in all phases of filling more commonly it is seen best in compression views When deformity is of maximum grade three or more scar pockets may form at the greater and lesser curvature sides of the base at the apex and elsewhere In such cases it



FIG 24 —Large ulcer crater posterior wall of slightly deformed duodenal bulb *A* the crater 2 cm in diameter and 1 cm in depth is brought into profile by turning the patient into the second oblique position *B* the crater *en face* *C* three years later the compressed bulb shows only moderate deformity at its apex

may be difficult to render judgment as to whether one or more crater may be present as well In Figure 25 *A* a central crater in the deformed bulb of a 34 year old male is shown by applying pressure over partially filled bulb Views *B* and *C* made six months after vagotomy show persistence of deformity but disappearance of the crater At no time was obstruction seen

*Ulcer crater in undeformed duodenal bulb* —When the bulb is undeformed an ulcer crater is easily overlooked unless compression is employed In the case illustrated in Figure 26 a 39 year old woman had had typical ulcer symptoms for three years The bulb was completely without deformity (*A*) Only when compression was applied was the central 1 cm crater demonstrated (*B*)

*Pyloric star*—Sometimes when an ulcer crater lies in the center of the base of the duodenal bulb very close to the pyloric canal it may be mistaken for a **pyloric star,** which is a fleck of barium that sometimes remains in the normal pyloric canal after the muscle has closed Figure 27 *C* shows such a pyloric star in a 68 year old woman there was no clinical reason to




Fig 25—Ulcer crater in deformed duodenal bulb *A* 5 mm ulcer crater at center of typical deformity demonstrated by application of pressure over partially filled bulb *B* and *C* six months later the crater is healed but deformity persists

Fig 26—Ulcer crater in undeformed bulb A filled bulb without compression *B* crater demonstrated by compression




FIG 27—Pyloric star simulating crater *A* ulcer crater in pyloric canal at base of bulb *B* three months later following management crater has healed *C* pyloric star no symptoms of duodenal ulcer The halo about the fleck is the contracted pyloric muscle *D* five months later no change in appearance

*suspect duodenal ulcer and the appearance had not changed when view D was made five months later* In another case however the central fleck seen at the base of the bulb (*A*) was diagnosed as crater and three months later following management and the subsidence of symptoms the fleck had disappeared (*B*)

*Coincidence of gastric and duodenal ulcer*—Infrequently these two lesions are seen in the same patient In the case illustrated in Figure 28 a 46 year old male had both an 8 × 8 mm gastric ulcer protruding from the lesser curvature of the body of the stomach just proximal to the incisura angularis and in addition a typical residual ulcer deformity of the duodenal bulb without crater or obstruction Following four months of medical management the gastric ulcer had healed without leaving a deformity *but the deformity of the duodenal bulb was unchanged* No special diagnostic problems are involved in such cases if one avoids the tendency to be satisfied with the finding of one lesion without looking carefully for a second

JEJUNAL ULCER

Following subtotal resection of the stomach X ray examination becomes more difficult because the barium passes through the stoma into the anastomosed jejunum The examination begin with the patient recumbent and ingesting small amounts of thick barium but sometimes a crater will fail to fill until the patient s erect and the gastric stump has been well filled with the ordinary barium mixture It seems logical that in connection with the anastomosis *blind pockets might be left which could retain barium* and simulate craters of jejunal ulcers but actually this does not occur In the case illustrated in Figure 29 a 54 year old male developed a large stomal crater which three months following vagotomy had disappeared completely A jejunal ulcer may be smaller than this one or much larger but regardless of size jejunal ulcers do not wipe away under the palpating hand

*Jejunal ulcer recurring after healing by management disappearing following vagotomy*—Like other peptic ulcers jejunal ulcers may heal under antacid therapy only to recur In the case illustrated in Figure 30 a 36 year old male developed a stomal crater following subtotal resection for stenosing duodenal ulcer Seven months later an enormous jejunal ulcer was found but after irradiation and two months of medical management it healed There was recurrence three months later at which time a vagotomy was performed Seven weeks after vagotomy the crater had healed again there had been no further recurrence ten years later




Fig 28—Occurrence of duodenal ulcer and gastric ulcer in the same patient View *A* mucosal relief view of 8 × 8 mm benign crater at the lesser curvature of the stomach *B* filled view made same date *C* same case typical ulcer deformity of bulb (The gastric ulcer healed in four months the bulb deformity persisted)

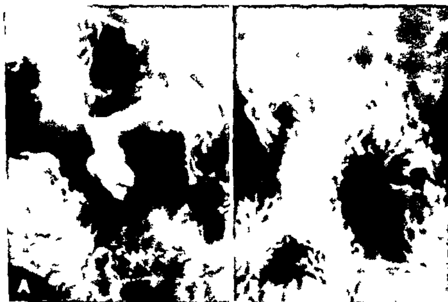



Fig 29—A jejunal ulcer before vagotomy *B* complete disappearance three months following vagotomy

X RAY THERAPY OF PEPTIC ULCER

If one accepts Schwartz s no acid—no ulcer dictum and believes that irradiation of the gastric fundus will reduce the production of hydro chloric acid he must agree that irradiation is a logical adjunct to antacid therapy All duodenal ulcer patients treated by us had medical management before irradiation and continued with it afterward and the gastric ulcer patients usually had in addition gastroscopy and more recently ex foliative cytology to reduce the danger of overlooking neoplasms among supposedly benign ulcers

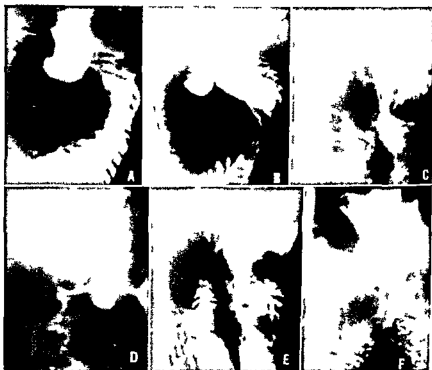



FIG 30—Recurrent jejunal ulcer *A* enormous 3 × 3 5 cm stomal ulcer *B* crater seen best with patient standing *C* following medical management and irradiation complete disappearance of crater *D* recurrence of crater *E* approximately seven weeks after vagotomy complete disappearance of crater *F* no recurrence of jejunal ulcer in ten years following vagotomy

PROCEDURE

Our therapy technique has varied with the years but for some time has been about as follows

1 Under fluoroscopic control the barium opacified gastric fundus is outlined in ink on the abdominal surface of the recumbent patient and then on the skin

of the back as he assumes the prone position in both cases with his arms in the position they will occupy during therapy

2 Rectangular 13 × 13-cm portals are inked anteriorly and posteriorly over the gastric fundus

3 Treatment is withheld until barium has left the alimentary tract (usually 24 hours)

4 Treatment is given daily for a total of ten days except for weekends or other unavoidable interruptions and in any event is completed within fourteen days

5 On each treatment day the radiation is delivered through both ports the dose to the fundus being 165 r a day for a total of 1 650 r The fundus is assumed to lie one third of the perpendicular distance from the skin of the anterior surface to the skin of the back in the left upper quadrant and except in unusually obese patients where the posterior dose may become excessive one delivers one half the gastric dose through the anterior port one half through the back

6 Factors 250 KVP 50 cm FSD 0 5 mm Cu 1 mm Al filter 1 5 mm Cu HVL

TABLE 1

EFFECT OF IRRADIATION ON GASTRIC ACIDITY AND HEALING

| Reduction in Acidity | No. of Patients | Failure of Ulcer to Heal | Recurrence | No Recurrence to Date |
|---|---|---|---|---|
| Less than 50 per cent | 53 | 2 | 20 | 31 |
| More than 50 per cent for less than one year | 45† | 0 | 13 | 32 |
| 50 per cent or more for one year or more | 15† | 0 | 5 | 10 |
| Total | 113 | 2 | 38 | 3 |

[illegible] acid studies a[illegible] patients [illegible] therapy
† Includes patients with achlorhydria

TABLE 2

TIME INTERVAL BETWEEN HEALING AND RECURRENCE

| Years | No. of Patients |
|---|---|
| 0– 1 | 13 |
| 1– 3 | 6 |
| 3– 5 | 7 |
| 5–11 | 12 |
| Total | 38 |

RESULTS

*Gastric ulcer* —Between 1937 and 1954 116 patients were treated by us —93 males and 23 females Seventy eight of the 116 were followed for five years or more Fourteen of the patients were less than forty years of age

and 70 were between forty and sixty Before irradiation all had had one or more recurrences on the usual antacid program The recurrence rate was reduced by irradiation there were no recurrences in 53 per cent of the patients Of the remainder some had recurrences some required surgery some could not be followed in only 6 7 per cent did the ulcer fail to heal In 43 of the 116 patients a temporary achlorhydria was produced During this period all the craters save one healed and no new craters appeared

*Duodenal ulcer*—A total of 113 duodenal ulcer patients were treated by us during the two years 1945 and 1946 and their progress has been followed from five to eleven years Prior to irradiation 86 of these patients had craters 95 had deformities and 15 showed varying degrees of stenosis All had symptoms of active ulcer 6 had intractable pain 72 night pain with an average duration of symptoms of eight years Results of irradiation are summarized in the two tables

Thirty four patients had 37 hemorrhages before irradiation and only four hemorrhaged after therapy had been completed Three patients had perforations before treatment none afterward Of the 113 irradiated patients 18 eventually had surgery and 8 have died In one of these the cause of death is unknown In the others it was unrelated to the ulcer Three of the 8 deaths were from cardiovascular disease one from prostatic disease one from cerebral metastasis presumably from bronchogenic carcinoma

JOSEPH B KIRSNER

# 6 Medical Management of Duodenal Ulcer Current Status

Peptic ulcer is one of the important medical problems of our time Its incidence is not known precisely but in the United States it is probably approximately 10 per cent The proportion of duodenal ulcer to gastric ulcer is 4 1 Although the ultimate cause or causes of peptic ulcer remain to be demonstrated much is known of the nature course and management of this disease There no longer exists any doubt as to the crucial role of hydrochloric acid in its pathogenesis Effective medical methods of treatment are available based upon control of the acid gastric secretion For those patients requiring surgery useful operative procedures have been developed

Peptic ulcer may be characterized physiologically as a consequence of the inability of localized areas of the stomach and duodenum to withstand the digestive action of acid gastric juice In gastric ulcer the output of hydrochloric acid is normal or low but its corrosive effect presumably surpasses the diminished resistance of the mucosa In duodenal ulcer the secretion of hydrochloric acid is excessive twofold to fourfold greater than normal and its digestive capacity exceeds the apparently normal resistance of the duodenal mucosa

The hypersecretion occurs at various times and for periods of varying duration—between meals during the night and after the ulcer has healed Its mechanism is not established completely Anatomically it seems to be

This chapter is composed of material constituting a report to the Council on Drugs American Medical Association published in *J A M A* 166 1727 April 5 1958

correlated with an increased number of parietal cells in the fundus and body of the stomach Physiologically histamine acetylcholine and hormonal factors including gastrin from the antrum and adrenocortical hyperfunction have received consideration Present evidence tends to emphasize the concept developed by Dragstedt and his colleagues of vagal hyperactivity acting upon a highly responsive gastric secretory mechanism other factors chemical and humoral probably are involved also

Peptic ulcer occurs only among individuals capable of secreting acid and only in those areas of the digestive tract exposed to hydrochloric acid the lower portion of the esophagus the stomach the first portion of the duodenum the jejunum in a patent gastroenterostomy and in a Meckel's diverticulum containing acid secreting gastric mucosa Most techniques for producing ulcers experimentally involve the overproduction of hydrochloric acid or interference with the usual mechanisms for neutralizing and buffering the acid The role of hydrochloric acid in the pathogenesis of peptic ulcer thus may be compared to that of the essential catalyst in a chemical reaction other ingredients (etiologic factors) are involved in the process but in the absence of the catalyst (HCl) the reaction cannot proceed

## TISSUE RESISTANCE

A priori tissue vulnerability localized or diffuse should be a significant factor in the development of peptic ulcer However little is known of the nature of tissue resistance Alterations in the rate of regeneration of epithelial cells in the mucous barrier and in the vascular supply to the stomach and duodenum may be important other mechanisms probably are involved but their identity is not known

In the absence of a specific cause the treatment of peptic ulcer emphasizes protection of the gastroduodenal mucosa from the digestive action of hydrochloric acid This objective probably would be accomplished by increasing tissue resistance However there is no satisfactory procedure for improving the defenses of the stomach and duodenum directly The resistance of the stomach and duodenum probably is enhanced indirectly by improving the general health of the patient by eliminating gastric irritants in food drink and medication (alcohol salicylates) and by removing excessive physical and emotional stress

## THERAPEUTIC OBJECTIVES

The complete elimination of hydrochloric acid would abolish peptic ulcer regardless of tissue susceptibility and other possible etiologic factors

However no method—pharmacologic medical or surgical except total gastrectomy—consistently produces complete and permanent anacidity hence no procedure per se regularly cures the disease Therapy emphasizes the effective neutralization or inhibition of hydrochloric acid and concurrent elimination of peptic activity The clinical objectives are relief of pain complete healing of the ulcer and the prevention of complications and recurrences

## DIET

There is no satisfactory evidence relating the usual peptic ulcer to abnormal protein metabolism or to a dietetic deficiency requiring special nutritional supplements Thus there appears to be no scientific basis in man for the use of the preparation Exul labeled as a mixture of extracts of cattle organs such as liver brains and adrenals together with dehydrated milk and cream choline hydrochloride vitamins and minerals The supplement Sustagen and similar preparations administered as a drink or intragastric drip provide additional calories and may buffer hydrochloric acid however they are not necessary when the intake and digestion of food are normal The ulcer patient is capable of eating a more liberal diet than has been advocated in the past Restriction of food does not necessarily cure peptic ulcer On the other hand dietary considerations provide a useful means of avoiding or relieving distress for certain foods may irritate the gastroduodenal mucosa and contribute to ulcer pain The dietary management of peptic ulcer consists in frequent feedings of bland foods avoiding mechanical chemical or thermal irritants providing adequate amounts of proteins carbohydrates calories minerals and vitamins and assisting in the neutralizing and buffering of the gastric contents The diet includes whole milk plus 22 per cent cream or Half and Half (12 per cent cream) taken as an equal mixture in quantities or 3 or 4 ounces hourly from 7 A M to 7 P M Chocolate malt and protein supplements may be added if a gain in weight is desired Skimmed milk may be substituted if the patient is obese In the absence of gastric retention additional food is administered in the form of six feedings daily The feedings initially are selected from the following items cooked cereals soft boiled eggs toast, butter strained cream soups custards puddings plain cookies Jello and ice cream After seven to ten days of complete relief from ulcer distress or sooner in the absence of obstruction the feedings are replaced by a three meal diet consisting of a substantial breakfast and noon meal and moderate supper a small feeding later in the evening also is permissible The meals are selected from the following list

*Cereals, grain products*

Cream of Wheat
Farina
Refined rice
Rice Crispies
Puffed rice
Rice flakes
Macaroni
Noodles
Spaghetti
Vermicelli
Corn flakes
Oatmeal

*Eggs*

Soft boiled
Soft scrambled
Soft omelet
Poached
Soft baked
Hard cooked

*Cheese*

Cream
American
Swiss
Cottage

*Milk, milk products*

*Buttermilk*
Milk
Cocoa
Ovaltine
Eggnog
Butter

*Breads*

*White bread or plain rolls*
Toasted white bread or rolls
Melba toast
Croutons
Bread sticks
Milk toast
Biscuits of white flour
Zwieback
Soda crackers, plain or *toasted*

*Soups*

Consomme
Chicken, broth or creamed
Vegetable
Cream of rice
Cream of potato
Cream of celery
Cream of tomato
Cream of asparagus
Cream of mushroom

*Fish, baked, creamed or broiled*

Salmon
Tuna
Whitefish
Cod
Haddock
Mackerel
Halibut
Flounder

*Beverages*

Tea
Sanka or Kaffe Hag
Coffee
Postum

*Potatoes*

Baked
Mashed
Au gratin
Escalloped
Boiled

*Cooked or canned fruits*

Bananas
Prunes
Peaches
*Applesauce*
Plums
Apricots
Pears
Baked apples (no skin)
*Pineapple*

*Raw fruits*

Bananas
Oranges
Grapefruit

*Cooked or canned vegetables*

Asparagus
String Beans
Carrots
Spinach
Sweet potatoes
Peas
Tomatoes

*Meats*

Crisp bacon
Chicken
Turkey
Beef
Lamb
Veal

*Desserts*

Custard
Floating island
Rice custard
Bread pudding
Tapioca pudding
Cornstarch pudding
Plain Jello
Cottage pudding
Angel food cake
Icebox cake
Plain cake
Ladyfingers
Sponge cake
Arrowroot cookies
Ice cream plain

*Miscellaneous*

Jelly
Marmalade

All foods should be well cooked and chewed thoroughly Several cups each of coffee and tea may be permitted daily The following foods should be avoided seasonings spices meat extracts alcoholic and carbonated drinks fried or very hot or very cold foods cabbage turnips corn nuts sausage pork and pork products except bacon

The intake of milk and cream is decreased gradually from hourly to two hour intervals and ultimately to between meals The bland three meal diet is continued indefinitely with further additions as indicated by the progress of the patient The casual suggestion to "watch your diet" or "avoid irritating foods is vague and ineffectual The program should be outlined clearly preferably in a printed list of those foods to be eaten and those to be avoided

## ANTACIDS

The purpose of antacid therapy is constant neutralization of the acid gastric content The ideal antacid theoretically should possess these advantages prolonged effective neutralization when administered orally in acceptable amounts absence of subsequent stimulation of secretion no untoward systemic effects such as alkalosis no cathartic or constipating action no interference with digestive or absorptive processes palatability and low cost These qualities are each desirable but they are not of equal

importance Serious toxic effects would obviate the usefulness of an otherwise potent antacid A preparation which does not cause constipation or diarrhea is still of secondary clinical value if it has little or no neutralizing action Effective neutralization is maintenance of the pH of the gastric content between 4 0 and 5 0 or higher at this hydrogen ion concentration acid and peptic activity are practically absent on the other hand healing may occur with less complete control of gastric acidity

The ideal antacid has not yet been synthesized Neutralizing efficiency in patients with duodenal ulcer is limited by the excessive rate of gastric secretion and by gastric emptying However many preparations are available which neutralize hydrochloric acid at least partially relieving pain and facilitating healing The most potent compound probably is calcium carbonate administered in quantities of 2 to 4 grams hourly during the day and evening (7 A M to 9 P M ) The principal disadvantage of calcium carbonate is constipation especially in older patients This usually can be corrected by substitution of the more laxative magnesium carbonate in amounts required by the individual case careful attention to bowel function is necessary with all types of antacid therapy Therapy with milk and calcium carbonate may be complicated infrequently by the hypercalcemic syndrome This disorder is characterized clinically by weakness headache distaste for milk and food and nausea and vomiting The chemical features are elevation of the serum calcium and blood urea nitrogen and temporarily depressed renal function This complication is more likely to occur in older patients with hypertension and pre existing impairment of renal function or when renal physiology is disturbed by gastrointestinal hemorrhage or electrolyte and fluid depletion The syndrome subsides rapidly after discontinuation of milk and alkali and the administration of isotonic saline glucose and water

Combinations of calcium carbonate with glycine or calcium caseinate do not appear to offer special neutralizing advantages Magnesium carbonate and magnesium oxide are potent antacids because of their laxative effect they are prescribed chiefly to counteract the constipating action of the ulcer regimen Tribasic calcium phosphate tribasic magnesium phosphate magnesium trisilicate magnesium hydroxide magnesium and calcium tartrate and dihydroxy sodium carbonate in doses of 2 to 4 grams hourly neutralize gastric acidity in varying degree A proprietary preparation combines tribasic calcium phosphate sodium phosphate and sodium citrate

Aluminum hydroxide aluminum phosphate and aluminum carbonate in doses of 8–16 cc alone and in various mixtures neutralize gastric acid its partially Their capacity to inactivate pepsin in vivo seems no greater than that of calcium carbonate the astringent demulcent and coating

properties attributed to them are not open to scientific measurement in man. Aluminum hydroxide increases the excretion of phosphate in the feces, however, the serum electrolytes are not altered. The constipating effect of aluminum hydroxide may be counteracted with magnesium trisilicate or magnesium hydroxide. Hydrated sodium aluminum silicate, "non reactive" aluminum hydroxide and aluminum dihydroxy amino-acetate do not appear to offer any special advantages.

Anion exchange resins are large insoluble bases with the capacity to absorb the anion of an acid forming an insoluble resin salt. In the alkaline intestinal contents the anion exchange is reversed and the resin is restored to its original state. Various resins alone or in combination with antacids are available; they may lower gastric acidity partially in man.

Bismuth salts and hog gastric mucin have no neutralizing value. Sodium carboxymethylcellulose alone or in combination does not offer any special advantages. Protein hydrolysates may decrease acidity temporarily but not impressively. The antacid effect of sodium bicarbonate is pronounced but transient; it is not prescribed because of the possibility of alkalosis when taken in large quantities, especially in patients with impaired renal function.

Many antacids are available also as tablets; these preparations contain aluminum hydroxide, magnesium trisilicate, calcium carbonate and magnesium oxide or magnesium carbonate in various quantities and alone or in mixtures; these compounds are also sometimes combined with resins, milk proteins and vitamins. Antacid tablets are inferior to powdered or liquid preparation because of the smaller amounts entering into reaction with the hydrochloric acid; however, rapidly disintegrating tablets may obviate this difficulty. Their principal usefulness is as adjunct antacid medication away from home or at work; their effectiveness is dependent upon adequate dosage. A compressed tablet (Nulacin) containing milk solids and alkali (magnesium trisilicate 3.5 grains, magnesium oxide 2.0 grains, calcium carbonate 2.0 grains and magnesium carbonate 0.5 grains) is also available. The tablet is kept between gum and cheek and allowed to dissolve gradually by continuous sucking; ten to sixteen tablets thus may be taken daily. This medication may neutralize acid more effectively than standard tablets but the amounts of antacid are very small. The continuous retention of a large tablet in the mouth may become a tedious ritual unacceptable to most patients.

Antacids act locally upon the gastric contents since they do not influence the acid secreting cells; their neutralizing effect is temporary and disappears when the medication is discontinued. The healing time of peptic ulcer may be prolonged and ulcers often recur, so that antacid therapy must be prolonged. The hourly schedule is continued until the ulcer has

healed completely. The antacid is then prescribed at intervals of two and three hours and subsequently once or twice between meals and during the evening; many patients maintain this latter program indefinitely. The administration of small quantities of mild antacids immediately after meals, a not uncommon practice, is impractical and ineffective since the food alone may neutralize acid during this period and the intervals between medication are too long. If antacids are to be prescribed only occasionally, they are more useful several hours after meals when the buffering effect of food has been dissipated.

Gastric acidity may be neutralized also by the continuous administration of milk and cream and alkali administered through an intragastric tube. One liter of milk containing 5 grams of sodium bicarbonate may be administered every eight hours. Another solution is prepared by mixing 100 cc of aluminum hydroxide or aluminum phosphate gel with 300–400 cc of warm tap water; it is administered at a rate of 15–20 drops per minute; 1,500–3,000 cc of the diluted suspension may be given in twenty-four hours. Food supplements may be given similarly as an additional source of calories for the nutritionally depleted patient. The intragastric drip may be maintained for the twelve-hour night period or continuously for as long as seven to ten days. The procedure has been recommended in patients with gastric hypersecretion and severe ulcer pain not controlled by ordinary measures and occasionally in the treatment of massive hemorrhage; it is contraindicated in the presence of pyloric obstruction.

## GASTRIC ANTISECRETORY COMPOUNDS

Diet and antacids do not control gastric acidity in peptic ulcer completely or continuously. Furthermore, many patients are reluctant to continue such a meticulous program indefinitely. Interest in anticholinergic medication is based upon the theoretical possibility of prolonged suppression of acid secretion, permitting a more liberal program. Anticholinergic drugs interfere with the transmission of nerve impulses mediated by acetylcholine at the neuro-effector junctions of postganglionic cholinergic nerves. Use of the drugs in peptic ulcer is based upon the concept that parasympathetic (vagal) hyperactivity is chiefly responsible for the gastric hypersecretion of duodenal ulcer and upon the expectation that these compounds will suppress the neurogenic mechanism. Actually, other phases of gastric secretion also may be influenced by these agents.

Tincture or powdered extract of belladonna in average doses does not inhibit acid secretion significantly in patients with peptic ulcer. Atropine sulfate, 0.5 mg (1/120 grain) three or four times daily by mouth, is partially effective; the same dosage given intramuscularly reduces the volume of secretion and the output of acid occasionally. Systemic manifestations

of parasympathetic inhibition are frequent with quantities which inhibit gastric secretion in man An additional effect of atropine and similar compounds in ulcer therapy may be to delay gastric emptying permitting a longer period of interaction between acid and antacid Synthetic atropine substitutes including Syntropan Novatrin Trasentine Dibuline and Bentyl hydrochloride among numerous preparations are less effective than atropine The quaternary ammonium compound tetraethylammonium chloride or bromide administered parenterally and hexamethonium iodide (one of the homologous series of polymethylene bistrimethyl ammonium compounds) prescribed orally may inhibit acid temporarily However these drugs cause disturbing side effects including postural hypotension and intestinal atony and thus are not recommended in ulcer therapy

Banthine temporarily suppresses gastric acidity when injected intramuscularly in doses exceeding 0 03 mg per kilogram body weight The antisecretory effect after oral administration is less impressive Single doses of 50 or 100 mg of Banthine by mouth may lower the volume of secretion however the concentration of hydrochloric acid is unchanged Banthine in quantities of 50 or 100 mg by mouth four times daily may provide symptomatic relief but side effects are common Peptic ulcer may recur during the use of Banthine patients occasionally appear to develop a tolerance to the medication The antisecretory effect of Prantal resembles that of Banthine however side effects are less frequent and 400–800 mg or more may be taken by mouth daily without apparent discomfort

Many new gastric antisecretory compounds have been developed These include Pamine (daily dose 15–30 mg ) Pro Banthine (75–240 mg ) Monodral (15–30 mg ) Antrenyl (40 mg ) Marplan (20–25 mg ) Malcotran (100–200 mg ) Pathilon (200 mg ) Darstine (400 mg ) Elorine (400–1000 mg ) Tricoloid (400–1000 mg ) Cotrainul (400 mg ) Piptal (25 mg ) Skopolate (6–12 mg ) and Tral (75–100 mg ) administered in divided amounts three to four times daily

Anticholinergic compounds are much more potent when administered intramuscularly than when administered orally but parenteral therapy except in occasional hospitalized patients is not practical Since it is more *effective against basal than against food stimulated secretion* the medication is taken before meals Increased amounts twofold or threefold larger than average are prescribed at bedtime in an effort to lower the excessive nocturnal gastric secretion Since the action of these drugs is limited to the period of administration they must be taken continuously Since the objective in peptic ulcer is prolonged inhibition of gastric secretion treatment is maintained for long periods of time The important considerations

healed completely The antacid is then prescribed at intervals of two and three hours and subsequently once or twice between meals and during the evening many patients maintain this latter program indefinitely The administration of small quantities of mild antacids immediately after meals a not uncommon practice is impractical and ineffective since the food alone may neutralize acid during this period and the intervals be tween medication are too long If antacids are to be prescribed only occa sionally they are more useful several hours after meals when the buffer ing effect of food has been dissipated

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## GASTRIC ANTISECRETORY COMPOUNDS

Diet and antacids do not control gastric acidity in peptic ulcer completely or continuously Furthermore many patients are reluctant to continue such a meticulous program indefinitely Interest in anticholinergic medi cation is based upon the theoretical possibility of prolonged suppression of acid secretion permitting a more liberal program Anticholinergic drugs interfere with the transmission of nerve impulses mediated by acetylcholine at the neuro effector junctions of postganglionic cholinergic nerves Use of the drugs in peptic ulcer is based upon the concept that parasympathetic (vagal) hyperactivity is chiefly responsible for the gastric hypersecretion of duodenal ulcer and upon the expectation that these compounds will suppress the neurogenic mechanism Actually other phases of gastric secretion also may be influenced by these agents

Tincture or powdered extract of belladonna in average doses does not inhibit acid secretion significantly in patients with peptic ulcer Atropine sulfate 0 5 mg (1/120 grain) three or four times daily by mouth is par tially effective the same dosage given intramuscularly reduces the volume of secretion and the output of acid occasionally Systemic manifestations

urine extracts of animal stomach duodenum and colon chlorophyll and cabbage juice Surface coating agents theoretically protecting the ulcer from hydrochloric acid such as emulsified methylopolysiloxanes have not been developed for clinical use

## GASTRIC ASPIRATION

*Nightly aspiration of the stomach with an Ewald or Levin tube is useful* in hospitalized patients with gastric retention since it removes a considerable quantity of acid content which otherwise bathes the ulcer contributing to its activity Gastric aspiration also is a very effective method of relieving severe ulcer distress The procedure furthermore may provide important information regarding the managment of patients with retention A decrease in the nightly aspiration to a volume of 3 or 4 ounces suggests inflammation edema and spasm *as the cause of the obstruction* rather than cicatricial stenosis Persistently large aspirates on the other hand indicate organic obstruction necessitating surgical treatment

## PHYSICAL FATIGUE EMOTIONAL STRESS

The admonition to "treat the patient as well as his ulcer is not a trite remark Excessive physical fatigue and prolonged emotional stress may increase the secretion of hydrochloric acid and the susceptibility of the gastroduodenal mucosa to injury Rest and relief of emotional tension consequently are important adjuncts in therapy The needs vary with the individual some patients can adjust their daily routine to obtain more rest without discontinuing their work others respond more effectively to a vacation away from home Hospitalization for several weeks is desirable in patients with persistent severe ulcer distress and especially in the management *of recurrent or complicated ulcers Hospitalization provides an op*portunity for careful regulation of therapy more thorough indoctrination of the principles of treatment and it removes the patient at least temporarily from the stress producing environment

Management of the emotional problems requires identification of the disturbing factors—domestic social or environmental—and then intelligent efforts at their control by avoidance "ventilation" of the problem reorientation of the patient *or the release of tension* in pleasant recreational activities The ultimate goals are the establishment of regular habits and a life of moderation" The support provided by the interested friendly yet objective physician may be very helpful in this regard Formal psychotherapy usually is unnecessary Mild sedation with phenobarbital 30 mg (½ grain) four times daily or elixir of triple bromides 4 cc (1 teaspoonful) four times daily promotes relaxation and rest sedatives at night are useful in insuring an adequate amount of sleep "Tran

in anticholinergic therapy are the use of *sufficient quantities and sustained* regular medication

No single anticholinergic compound excels in gastric inhibitory capacity clinical tolerance and therapeutic value although several appear to be more effective than the majority these include Pamine Pro Banthine Monodral Milcotran Tral and several additional compounds now under study In general the drugs lowering acidity most effectively also tend to produce systemic manifestations of parasympathetic inhibition The symptoms include dryness of the mouth blurring of vision constipation slowing of the urinary stream headache drowsiness heartburn tachycardia choking sensation and mental confusion The ideal gastric antisecretory agent suppressing acidity for long periods of time after oral administration without development of tolerance and with minimal or no side *effects thus remains to be synthesized Present compounds do not produce* a true "medical vagotomy However they surpass belladonna atropine Banthine and Prantal Administered orally several preparations may decrease acid secretion at least temporarily As adjuncts to antacids they probably facilitate more efficient neutralization of the gastric contents and in occasional patients at least they may benefit not only the immediate but also the long term treatment of peptic ulcer On the other hand their value in preventing the complications of peptic ulcer and in decreasing the need for surgery has not been established The use of anticholinergic drugs alone in the management of peptic ulcer is not recommended These compounds are contraindicated in the presence of pyloric obstruction incipient glaucoma prostatic hypertrophy and cardiospasm

INEFFECTIVE COMPOUNDS

The available antihistaminic compounds do not lower gastric acidity significantly in man and are of no value in the treatment of peptic ulcer Endocrine preparations including parathyroid extract posterior pituitary extract enterogastrone urogastrone sex hormones and desoxycorticosterone acetate do not reduce gastric acidity significantly in patients with duodenal ulcer Compounds inhibiting the enzyme carbonic anhydrase lower the output of hydrochloric acid after intravenous administration under experimental conditions However carbonic anhydrase inhibitors *such as acetazoleamide (Diamox) orally have not proved of practical* value in the management of duodenal ulcer

In the absence of a specific cure the number of alleged ulcer remedies remains enormous Many have been discredited Current evidence indicates that the following substances should also be discarded as useless in ulcer therapy detergents such as sodium alkyl sulfate urea formaldehyde resins thixotropic gel bile salts histidine extracts of pregnant mares

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quilizing drugs also are prescribed for this purpose alone or together with anticholinergic medication They are useful in occasional patients but do not appear to have any special advantages in ulcer therapy per se Chlorpromazine in large amounts may decrease gastric secretion on the other hand reserpine in large quantities orally may increase the output of hydrochloric acid

## IRRADIATION OF THE STOMACH

Mild roentgen irradiation of the stomach may be utilized as adjunct therapy for the purpose of decreasing or suppressing completely the secretion of hydrochloric acid Approximately 1 600–2 000 roentgen units total depth dose are directed in ten divided applications to the fundus and body of the stomach over fluoroscopically outlined anterior and posterior portals The inhibitory effect of irradiation upon gastric secretion depends upon the destruction of parietal cells The development of anacidity is followed invariably by complete healing of the ulcer and by no recurrence for the duration of anacidity Although the degree of secretory inhibition is quite variable the clinical course often seems distinctly benefited Harmful effects have not been observed Gastric irradiation also has been combined with the surgical procedure of antroduodenectomy approximately two months after operation a depth dose of 2 000 r is delivered in divided amounts over a period of three weeks The cobalt 60 teletherapy unit has been utilized recently for gastric irradiation its advantages reportedly include skin sparing effect and greater depth dose

## TOBACCO ALCOHOL AND ULCEROGENIC DRUGS

There is no conclusive evidence at present that average smoking increases gastric secretion significantly The use of tobacco by ulcer patients is dealt with most practically on an individual basis Moderate smoking seems harmless in many instances Excessive smoking on the other hand is undesirable perhaps because of the decreased intake of food and diminished neutralization of gastric acidity In such instances the habit should be discouraged the recommendation of complete abstinence is preferable to the ineffectual suggestion to decrease the quantity of tobacco Excessive smoking ordinarily reflects increased nervous tension the important problem therefore is relief of the emotional stress

Alcohol tends to increase the secretion of hydrochloric acid its use therefore should be avoided Excessive drinking of coffee may irritate the gastroduodenal mucosa and reactivate peptic ulcer Numerous medications may increase gastric secretion irritate the stomach and duodenum and predispose to the recurrence or new development of peptic ulcer with bleeding These compounds include salicylates corticotropin prednisone

and prednisolone phenylbutazone (butazolidin) and reserpine they should be avoided if possible in patients with known peptic ulcer or administered in conjunction with antacids

## COMPLICATIONS

### INTRACTABLE OR REFRACTORY PEPTIC ULCER

The term intractable ulcer" implies a lesion not responding to the usual treatment and therefore requiring operation Intractability is interpreted differently and not necessarily critically by all observers and "usual therapy" is not synonymous with effective treatment The program prescribed in an individual case may be inadequate or the patient may not adhere to the regimen because of a poor patient physician relationship Many cases classified as intractable undoubtedly belong in this category the ulcer itself is not refractory for under proper circumstances it heals completely In the truly intractable peptic ulcer treatment that is ordinarily effective fails to promote healing or to prevent complications The underlying cause may be serious emotional difficulties uncontrollable gastric hypersecretion decreased tissue resistance or irreversible complications such as obstruction or penetration of the ulcer with adherence to the pancreas In evaluating an "intractable" peptic ulcer then careful study of all possible contributory factors is necessary

### GASTRIC RETENTION

In patients with peptic ulcer gastric retention usually is attributable to inflammation and edema adjacent to an active ulcer temporarily narrowing the channel through the pylorus and duodenum This complication often responds within seven to ten days to a medical regimen of nothing by mouth continuous gastric aspiration and the parenteral administration of electrolytes and fluids The continuous removal of acid permits the ulcer to heal the edema and inflammation subside and the channel through the pylorus and duodenum once more is patent as indicated by decreasing volumes of gastric aspirate The use of antispasmodic and anticholinergic compounds under these circumstances is undesirable for the subsequent decrease in gastric motility may intensify the retention In perhaps 15 per cent of cases with retention the obstruction is caused by scarring and cicatricial narrowing of the pylorus and duodenum this problem requires surgical treatment

### ACUTE PERFORATION

This is the most urgent indication for operation Surgical treatment usually is limited to simple closure of the perforation though in patients with

a long history of ulcer recurrence who are in good condition partial gastric resection also may be performed

Excellent therapeutic results apparently may be obtained with a program including prompt continuous and effective gastric aspiration the administration of adequate amounts of electrolytes glucose and water plus sulfonamides antibiotics and supportive care The non operative approach is based upon the observation that early perforations will seal rapidly if the stomach is emptied and kept so by aspiration It seems to be indicated especially in patients with difficult medical problems who are serious operative risks

MASSIVE HEMORRHAGE

Hemorrhage complicates the course of peptic ulcer in perhaps 20 or 25 per cent of all cases some patients appear to have a definite tendency to recurrent bleeding Therapy usually is medical It includes rest in bed and sedatives such as sodium luminal (2 grains intramuscularly every four to six hours) for restlessness The blood type of the patient is determined and blood is made available immediately The hemoglobin and erythrocyte count or the hematocrit are measured daily or as often as the clinical course indicates If the patient is vomiting food and drink are withheld until the vomiting subsides Otherwise milk and cream and antacids are administered hourly during the day as in the standard program the alkali is continued every two hours during the night Transfusions of whole blood 500–600 cc are administered when the systolic blood pressure falls to 100 the pulse rate exceeds 100 and the erythrocyte count decreases to below three million or in continued severe hemorrhage regardless of any criteria Five per cent glucose in isotonic saline may be administered in limited quantities subcutaneously Additional measures may include the administration of antisecretory drugs and infrequently the intragastric drip The antacid program is maintained until the erythrocyte count and hematocrit are stabilized and the feces are negative for occult blood The treatment subsequently is that outlined for uncomplicated peptic ulcer

Surgery is indicated in bleeding peptic ulcer under the following conditions (1) severe persistent hemorrhage during medical treatment (2) recurrent bleeding (3) stomal ulcer with hemorrhage (4) hemorrhage and perforation and (5) hemorrhage and pyloric obstruction The decision for operation usually is made during the first 48–72 hours because complications and mortality rate rise with persistent uncontrolled hemorrhage Occasionally the decision may be deferred for several additional days provided the patient s general condition remains good and an adequate blood volume is maintained Bleeding is more severe and more like

ly to persist in patients fifty years of age and older operation therefore is indicated when these patients do not respond promptly to medical treatment A useful index is when two or more transfusions per day or during a portion of a day are insufficient to replace the blood lost and the bleeding continues (the so called test of transfusion) Since the hazards of surgery are also increased in this age range the surgeon must accept a higher calculated risk The operation of choice in massive hemorrhage from peptic ulcer is partial gastric resection excision of the lesion if possible and ligation of the bleeding vessel Gastroenterostomy alone or with vagotomy usually is not satisfactory for this purpose "Blind gastric resection may be performed to control bleeding from tiny gastric erosions so small as to escape recognition clinically or at operation Excellent results have been reported however opinions vary as to the routine applicability of the procedure Surgery does not protect completely against recurrent hemorrhage although the possibility is greatly reduced

#### JEJUNAL ULCER

Here a difficult therapeutic problem is presented because of the tendency of the lesion to penetrate bleed and perforate Some patients respond to careful medical management in the hospital including roentgen irradiation of the stomach As a rule however surgery is preferred transabdominal vagotomy with or without further gastric resection depending upon the circumstances

#### GASTROJEJUNOCOLIC FISTULA

This requires initially the restoration of nutrition with a diet high in proteins calories and supplements and the correction of electrolyte and fluid imbalance The operative procedure consists in resection of the fistula reconstruction of the gastroenterostomy and a more adequate gastric resection or vagotomy

### PREVENTION OF RECURRENCES

The immediate results of effective therapy in peptic ulcer are good with prompt relief of pain and complete healing The long term results are less encouraging perhaps because of failure to maintain adequate and continuous neutralization of the acid gastric content Recurrences of peptic ulcer are frequent with almost any type of therapy whether medical or surgical which does not abolish acid secretion permanently The precipitating factors recognized and emphasized most often are physical fatigue emotional stress dietary indiscretions irritating drugs and intercurrent illness There are no specific measures completely protecting against recurrences so long as acidity remains however the frequency and severity

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HENRY N HARKINS
AND
ROBERT V DE VITO

# 7 *Surgical Procedures for Duodenal Ulcer Indications and Rationale*

The surgical treatment of duodenal ulcer is essentially the treatment of the complicated and intractable case Although this chapter is written by surgeons, the experiences of the senior author with such outstanding gas troenterologists as Palmer and Kirsner at Chicago Paulson of Baltimore and Volwiler and Rubin of Seattle have served to emphasize this point Operative intervention is indicated in only about 15–25 per cent of duo denal ulcer cases This does not mean however that surgery when it is indicated is in any way unimportant or optional In the refractory case of duodenal ulcer surgical treatment is often urgently needed and it is usually the best, if not the only alternative

The chief indications for surgical treatment of duodenal ulcer are five in number obstruction intractability in spite of adequate medical ther apy incompatibility of medical therapy perforation and massive hemor rhage The problem of carcinoma seldom enters into the indications for duodenal ulcer surgery The difference between the second and third in dications above is an important one A conscientious patient who has con trol over his time schedule yet is unsuccessful with his medical treatment falls into the second indication an irresponsible patient or one with ir regular or rigid working conditions which may not permit adherence to a plan of medical therapy falls into the third category

The surgical treatment of duodenal ulcer is at a crossroads In 1939 in practically all modern clinics partial gastric resection usually *ad modum* Billroth II was the operation of choice Today in 1959 the picture is not quite so simple The pioneer physiologic observations of Dragstedt

of recurrences may be reduced by a comprehensive program including (1) thorough treatment of the initial lesion and careful subsequent supervision of the patient (2) education of the patient as to the nature of the disease and the principles and objectives of treatment (3) continued use of a bland diet (4) a practical but efficient program of acid control (5) the avoidance of alcohol tobacco and irritating drugs (6) sufficient rest and sleep (7) control of emotional problems if possible and (8) proper care of respiratory infections and other intercurrent illness

Despite the limitations of medical management current methods of treatment when applied properly are effective in the vast majority of patients with uncomplicated peptic ulcer Treatment should not be confined to a single therapeutic measure The emphasis should be on total management including antacids anticholinergic drugs sedatives avoidance of gastrointestinal irritants and trained attention to emotional problems *Inadequate results usually are attributable to inadequate therapy* The fact that treatment is more or less non specific does not justify its casual and indifferent application The continued study of hormonal factors of drugs acting upon enzyme systems implicated in the process of gastric secretion and of secretory inhibitors in the gastric content eventually may yield a medical technique for producing sustained gastric anacidity The cure of peptic ulcer obviously will depend upon further knowledge of the nature of tissue resistance and the mechanism of secretion of hydrochloric acid These objectives may seem unattainable but in view of the remarkable advances in medicine achieved in our lifetime they should not be regarded as impossible

No one can foretell whether any one of these operative procedures will outstrip the others in preference by 1969—or which one it will be if this does occur—or whether some new operation will come into prominence perhaps from among the miscellaneous technics scarcely noticed but in occasional use today It is possible that some new non surgical method will be the procedure of choice for complicated and intractable ulcer ten years hence

The plan of this chapter will be to discuss the indications and rationale for the above operations considering the physiology of gastric secretions and the pathogenesis of duodenal ulcer We will first discuss intractable duodenal ulcer in general and then the special indications for the treatment of cases with perforation and cases with massive hemorrhage

## SURGICAL TREATMENT OF DUODENAL ULCER

### HISTORICAL

Billroth performed the first successful partial gastric resections in 1881 with gastroduodenal anastomosis and in 1885 with gastrojejunal anastomosis His pupil Wolfler did the first successful gastrojejunostomy in 1881 Until the time of World War I the Billroth resections were applied mainly to gastric ulcer—and of course carcinoma—while the Wolfler gastrojejunostomy was the operation of choice for duodenal ulcer The work of Strauss of Berg and of Lewisohn in this country and of von Haberer in Germany during or shortly after World War I swung the tide of interest to gastric resection for duodenal ulcer There was a great lag in the general acceptance of gastric resection particularly in the United States In some schools and clinics the adoption did not take place until the time of World War II however by then it had long been the operation of choice for duodenal ulcer in the more advanced clinics Gastrojejunostomy was used in some cases but it was a second choice In 1943 Dragstedt and Owens introduced vagotomy Later a drainage procedure was added (gastrojejunostomy Dragstedt and Woodward 1951 Heineke Mikulicz pyloroplasty Weinberg 1956) It is often stated that vagotomy was used by many before Dragstedt s pioneer work but such "vagotomies were invariably either incomplete or so low on the stomach as to be ineffective as far as the parietal cell area of the corpus is concerned or so high in the neck that they affected other vital organs as well as the stomach At any rate during the ten years following 1943 these two operations—partial gastric resection on the one hand and vagotomy plus drainage procedure on the other—vied for popularity as the operation of choice for complicated duodenal ulcer

Wangensteen and other surgeons as well as those of physiologists have helped reopen the entire issue The chief contenders for pre eminence as the operation of choice for duodenal ulcer are now as follows (see Fig 1)

1 Partial gastric resection (Billroth I)
2 Partial gastric resection (Billroth II)
3 Hemigastrectomy and vagotomy (Billroth I)
4 Hemigastrectomy and vagotomy (Billroth II)
5 Vagotomy and gastrojejunostomy (Dragstedt)
6 Vagotomy and pyloroplasty (Weinberg)
7 Segmental resection of the corpus and pyloroplasty (Wangensteen I)
8 Segmental resection of the corpus pyloroplasty and vagotomy (Berne Mikkelsen)

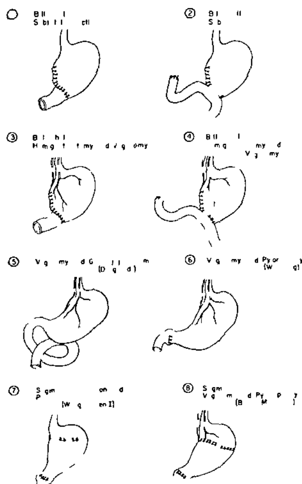


Fig 1 —Surgical treatment of duodenal ulcer

sequently may be returned to control levels by Finney pyloroplasty (Nyhus *et al* 1954)

10 Vagotomy reduces secretory response to the administration of histamine (Oberhelman and Dragstedt 1948)

11 Stimulation of the anterior hypothalamus produces a drop in the pH of gastric content in monkeys (Porter *et al* 1953)

12 Chronic electrical stimulation of midline hypothalamic areas in monkeys produced gastroduodenal lesions in 8 of 19 monkeys (French *et al* 1957)

13 Chronic electrical stimulation of preoptic and medial portions of the anterior hypothalamus produces increased acidity of gastric secretion from pouches in cats together with frank ulceration (Sen and Anand 1957)

*Role of the Antrum*

1 Intravenous injection of antral extract produces increased acid secretion (Edkins 1906)

2 Antral excision reduces acid secretion from Pavlov and Heidenhain pouches (Woodward *et al* 1950)

3 Antral transplants to the colon markedly stimulate acid secretion from gastric pouches (Dragstedt *et al* 1951) if the vagus nerves to the antrum are cut (Jones *et al* 1958) If a rim of acid secreting mucosa is incorporated as part of the antral pouch hypersecretion does not occur (Oberhelman *et al* 1952)

4 Partial resection of the antrum either from the stomach or from antral pouches transplanted to the colon produces a decrease in Heidenhain pouch secretions with the decrease related to the amount of antral tissue removed (Oberhelman *et al* 1952)

5 If an innervated isolated antral pouch is stimulated mechanically by balloon distention there is an acid secretion response from a Heidenhain pouch This secretory response is blocked by simultaneous perfusion of the isolated antrum with N/10 HCl and is potentiated in the presence of alkaline pH (Woodward *et al* 1957)

6 Crude liver extract or ethyl alcohol perfusion of the isolated antral pouch produces a secretory response which is not enhanced by alkaline pH but is abolished by acid pH (Woodward *et al* 1957)

7 Antrum motility per se either by vagal efferents or by intrinsic plexuses stimulates gastrin release (Dragstedt *et al* 1953 Oberhelman *et al* 1957 Woodward *et al* 1957)

8 Submucosal dissection of the antrum (Jones *et al* 1957) or removal of the seromuscular coat from the antrum (Baugh *et al* 1958) results

PHYSIOLOGIC FACTORS IN PEPTIC ULCER

The products of gastric secretion include hydrochloric acid pepsin and mucin The most important of these is probably the hydrochloric acid because its secretion as free acid varies in disease and since without it pepsin would be inactive because of improper pH Mucin acts to lubricate and protect the gastric rugae and duodenal wall

The site of secretion of these substances is of importance in planning certain operative procedures on the stomach Hydrochloric acid is secreted mainly by the parietal cells of the corpus there are a few parietal cells in the fundus but essentially none in the antrum Pepsin is secreted by the chief cells of the corpus Mucin is secreted by all parts of the stomach but particularly by the antrum Brunner s glands of the first portion of the duodenum also secrete a great deal of mucin

There are many factors which may directly or indirectly affect the quantity of gastric acid secretion and thus contribute to the pathogenesis of peptic ulcer Below is given a partial summary of selected recent work on certain of these factors—the role of the vagus nerves antral activity and duodenal inhibition—plus an analysis of the relative sensitivity of different portions of the gastrointestinal tract to peptic ulceration

*Role of the Vagus Nerves*

1 Vagotomy eliminates the conditioned secretory response of the stomach (Pavlov 1910)
2 Sectioning of the vagi to a total stomach or Pavlov pouch causes a reduction in acid secretion (Dragstedt *et al* 1950)
3 Vagotomy entirely eliminates peptic ulceration in the Shay rat (Harkins 1947) by depressing gastric secretion (Alexander and Merendino 1952)
4 Adequate doses of Banthine or atropine also abolish peptic ulceration in the Shay rat (Sauvage and Harkins 1951)
5 Vagotomy in the Mann Williamson preparation markedly decreases the incidence of stomal ulceration (Harkins and Hooker 1947)
6 Banthine and atropine decrease the incidence of stomal ulceration in the Mann Williamson preparation (Sauvage and Harkins 1951)
7 Banthine or atropine markedly reduce the secretory response to histamine stimulation but do not alter the Heidenhain pouch secretory response to feeding (Sauvage and Harkins 1951)
8 Section of the vagus nerves to the stomach in the Sauvage preparation decreases the incidence of stomal ulceration (Sauvage *et al* 1953)
9 Section of the vagus nerves to the main stomach causes an increase in Heidenhain pouch secretion (Storer Schmitz *et al* 1952) which sub

4 After antral resection the frequency of histamine induced ulceration is 88 per cent with gastrojejunostomy 38 per cent with gastroduodenostomy (Harkins and Nyhus 1956)
5 Intraduodenal pH of less than 2 5 is accompanied by a decided diminution in the volume and acidity of Heidenhain pouch secretions (Jones and Harkins 1958)

*Relative Sensitivity of Different Portions of the Gastrointestinal Tract to Peptic Ulceration*

1 Matthews and Dragstedt (1932) demonstrated that anastomosis of isolated gastric pouches to progressively more distal levels of the gastrointestinal tract was attended by a progressively higher incidence of stomal ulceration McMaster (1934) obtained similar results by anastomosing the total stomach rather than a pouch
2 Following a 75 per cent gastric resection with Billroth II reconstruction the incidence of stomal ulcer increases as the length of the afferent loop is increased (Merendino *et al* 1945)
3 While the above would indicate a graded sensitivity of the small bowel to peptic ulceration Kiriluk and Merendino (1954) demonstrated that there is no significant differential sensitivity to acid peptic solutions in the duodenum jejunum or ileum The stomach is relatively resistant and the esophagus particularly sensitive to acid peptic injury The most proximal duodenum deserves special consideration this area containing Brunner s glands is specifically resistant (Griffith and Harkins 1956 Dillard and Merendino 1956)
4 A progressive decrease in the pH and in the buffering capacity of small bowel contents is demonstrable as the distance from the pylorus is increased This factor presumably accounts for the increased frequency of stomal ulceration in distal anastomoses (Kiriluk and Merendino 1954)
5 When gastric pouches are drained into progressively distal segments of bowel which in turn have been interposed between transected ends of the duodenum with its neutralizing alkaline juices no stomal ulcerations occur (Dillard and Merendino 1956)

In summary physiological studies demonstrate that secretion of acid is stimulated by the vagi presumably with hypothalamic centers involved in the mechanisms of vagal excitation and by the gastric antrum which secretes a hormone in response to peristalsis distention and alkaline pH Acid production is reduced by two auto regulatory mechanisms—a low pH in the antrum "turns off gastrin production and a low pH in the duodenum reduces acid secretion by unknown mechanisms

in profound depression of twenty four hour Heidenhain pouch secretions

9 Studies of the secretory response to gastrojejunostomy (Zubiran Dragstedt *et al* 1952) demonstrated that gastrojejunostomy to the main stomach produces an increase in free acid secretion from the Heidenhain pouch if the stoma is high on the greater curvature If the stoma is large regardless of whether it is high central or low on the stomach it results in pouch hypersecretion (Kanar Schmitz *et al* 1953 Kanar Nyhus *et al* 1953 Stevenson *et al* 1957) Antral hyperfunction is the basis for this secretory response as shown by abolition of the response when antroneurolysis is performed (Jones De Vito *et al* 1958)

10 Antrumectomy in the Sauvage pouch reduces the incidence of peptic ulceration from 100 per cent to 45 per cent that is in this pouch preparation antrumectomy alone is more effective than vagotomy alone (Sauvage *et al* 1953)

11 Histamine induced peptic ulceration is increased in frequency if the antrum is excised (State *et al* 1955)

12 Studies by Harrison and associates (1956) further suggest an inhibitory mechanism of the antrum If 50 per cent of the antrum is transplanted as a pouch to the colon resection of the remainder brings a rise in Heidenhain pouch secretion Another group (Jordan *et al* 1957) prepared dogs with two separate antral pouches in addition to a *Heidenhain pouch Injection of histamine or alcohol perfusion* of one antral pouch caused the gastric pouch to secrete normally when the second antral pouch was then perfused with acid the gastric secretory response was blocked after a latency period of one to three hours Dragstedt s group performed almost identical experiments but could not demonstrate any inhibitory mechanisms of the antrum (Longhi *et al* 1957)

*Role of Duodenal Inhibition*

1 Gastroduodenostomy (three types) in dogs provides less Heidenhain pouch stimulation than does gastrojejunostomy (Harkins *et al* 1955)

2 Pyloroplasty (three types) in dogs produces essentially no increase in Heidenhain pouch acid secretion (Harkins *et al* 1955)

3 With the antrum transplanted to the colon Heidenhain pouch acid secretion is greater with a gastrojejunostomy than a gastroduodenostomy (Stevenson 1956) The incidence of stomal ulcer is likewise greater in the gastrojejunostomy dogs (66 per cent versus 25 per cent Harkins and Nyhus 1956)

On September 1 1955 we had completed a series of over 250 Billroth I operations for duodenal ulcer We considered that such a series was large enough for study and that it would be best to study these cases before increasing the number of cases As a result and because we were also intrigued by the operation of vagotomy plus hemigastrectomy we have adopted a combination of these plus the Billroth I type of anastomosis as our more or less official procedure Our selection is based not on dissatisfaction with the Billroth I (75 per cent resection) but on the total physiologic considerations stated above We are very pleased with the new combination operation and we have hopes that it may give even lower recurrence rates along with a decreased incidence of dumping However we have not yet performed enough operations to draw definite conclusions particularly since the follow up period has been so brief We have approximately 90–100 cases of the new combination

Also since we are receiving a fair share of our perforated ulcers and since we are somewhat fearful of opening the mediastinum to do a vagotomy we are continuing in these cases to do the Billroth I with 75 per cent resection without vagotomy

The difference between our recurrence rate which is less than 4 per cent even including unproven cases and the much higher rates reported by Ordahl (1955) and Goligher (1956) calls for a reassessment of the factors involved A number of possible explanations for this difference might be appropriately considered here

First it is likely that a difference in the extent of resection is a basic factor The senior author has seen some of the British gastric resections and does not believe they are always as radical as they might be This criticism does not apply to all however many such as Tanner do a quite adequate resection In this country also many do 40 per cent resections under the impression that they are removing 70 per cent of the stomach again many others do a more complete removal That the difference in results might be so explained was suggested during the report of Ordahl s original work (see Ross and Meadows 1952) presented at a meeting of the Society of University Surgeons in 1952 our own preliminary paper was presented on the same program In the discussion a considerable point was made of the fact that Ordahl s results were much better than ours in that they had no dumping whereas we had considerable dumping I am sure that this is partly related to the fact that they might not have been doing adequate resections Their observation that they never needed to mobilize the duodenum is at least circumstantial evidence for the same point

It has also been suggested that our lower rate of recurrence is an artifact based on inadequate follow up studies The very fact that we have

The Billroth operations are designed to remove the ulcer (in most cases) to remove the major portion of the parietal cell mass and to remove the antral stimulatory mechanisms Vagotomy serves to abolish the cephalic phase of acid secretion but when done alone may be attended by persistent high acidity because of secondary accentuation of the gastric phase of acid secretion For this reason vagotomy must be supplemented by resection of the antrum or by a drainage procedure in the form of gastrojejunostomy or pyloroplasty With the above considerations in mind three basic types of duodenal ulcer surgery emerge adequate resection vagotomy plus antrumectomy and vagotomy plus drainage procedure

If a resection procedure (with or without vagotomy) is done should the reconstruction be by gastroduodenostomy or by gastrojejunostomy? If vagotomy plus drainage procedure is chosen should the drainage be a pyloroplasty or gastrojejunostomy? Experimental data indicate that gastroduodenal continuity is desirable in order to maintain the regulatory mechanism of duodenal inhibition to abolish antral hyperfunction if the *antrum is retained and to gain the neutralizing advantage of duodenal* juices

Evidence that the antrum may also function actively to inhibit acid secretion has led to the development of a fourth type of procedure—seg*mental resection of the fundus (Wangensteen 1958) This procedure* is designed to remove the major parietal cell mass while retaining the antrum in continuity and preserving a relatively large gastric cavity A pyloroplasty is also done since the pylorus is vagotomized by the transection of the stomach A further development of the same principle (Berne Mikkelsen) adds total gastric vagotomy These are well founded on physiologic data with one reservation—one wonders whether the antral inhibitory mechanisms which are preserved by leaving the antrum in place will prove to be of greater value than elimination of the stimulatory mechanisms by antrum removal The future course of patients with these procedures should be of interest to all surgeons

## SELECTING AN OPERATIVE PROCEDURE

A summary of the factors in selection of the operation for duodenal ulcer in general should emphasize that such a selection will depend more and more in the future upon physiologic considerations regarding gastric secretion However the problem is not quite so simple as merely preventing stomal ulcer by cutting down *the secretion of free acid Dumping and* the other postgastrectomy syndromes are to be reckoned with and the surgeon must chart his course between the Charybdis of stomal ulcer and the Scylla of dumping

*In our own* clinic selection has been guided by the following factors

Roscoe Graham and others simple closure was so popular that in 1949 it had virtually no rivals However since that time there has been an awakened interest in immediate resection among English speaking surgeons on both sides of the Atlantic (Lowdon 1952 Emmett and Owen 1953 Jones and Doll 1953 Moore Harkins and Merendino 1954 Cooley Jordan Brockman and DeBakey 1955 Taylor 1957)

More interesting however has been the interest developed independently in England and the United States in continuous aspiration Probably the first to use this mode of therapy were Lane in Detroit (1931) and Mullen in Seattle (1939) The first reports in the literature were made by Bedford Turner (1945) Taylor (1946) and Visick (1946) all in England In this country Seeley (1949 1951) has developed increasing interest in this method

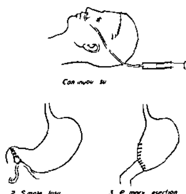



Fig 2 —Management of perforated duodenal ulcer

In brief therefore while in 1949 simple closure was the method of choice for the treatment of perforated peptic ulcer in 1959 three methods are popular (1) continuous aspiration (2) simple closure and (3) definitive early subtotal gastric resection (see Fig 2)

MANAGEMENT OF PERFORATION

*Continuous Aspiration* —The *sine qua non* of the aspiration (or suction) method is that it be continuous To accomplish this end Taylor advocates after a preliminary X ray and other diagnostic measures that the nurse aspirate the stomach with an ordinary hand syringe and record immediately on the chart the amount removed repeating this every quarter hour at first and later every half hour Taylor adds We prefer this method to suction by mechanical pumps because too much reliance is apt to be placed on the latter when they fail some time may pass before this is noticed If the nurse has to aspirate the catheter by hand and write down

found considerable dumping in our follow ups indicates the thoroughness with which we have questioned these patients As to the number of follow ups it must be admitted that because of our type of patient we do not see a large percentage of them afterward We make every effort to complete a case with follow up study we send out hundreds of letters every year the social service department and the police work with us in tracing these patients and we are helped by Dr Volwiler and his Division of Gastroenterology

Still another explanation of the higher incidence of ulcer recurrence elsewhere may be that some of these cases are not actually recurrences To elaborate we now take an X ray of the stomach remnant before our patients are discharged from the hospital noting any irregularities or niches in the lesser curvature closure We find these quite frequently and they are useful as a base line for future X rays but they might easily be mistaken for new ulcerous lesions Goligher s paper (1956) for instance suggests that several of his so called recurrences may have been such irregularities Reoperation of several of our patients with such niches has revealed no ulcer even with complete opening and inspection of the stomach remnant

It is our hope that the true status of the Billroth I operation for duodenal ulcer will be determined within the next few years We did not originate this procedure and are as anxious as anyone that the truth—favorable or unfavorable—be brought out into the open

## PERFORATED PEPTIC ULCER

Perforated peptic ulcer represents one of the most serious complications of this disease While perforation of gastric ulcer is probably relatively more serious in absolute numbers of deaths perforation of duodenal ulcer still leads by a slight margin If the death rate of 1953 is continued 125 000 persons now alive in the United States will die of perforated peptic ulcer

### HISTORICAL

The first surgical treatment of perforated ulcer by simple closure was performed by Mikulicz in 1897 with death following in three hours In 1899 Keetley of London performed the first partial gastrectomy utilizing the Billroth I technic with recovery Von Haberer (1919) first advocated the general use of immediate resection Judine (1939) reported 937 cases mostly *ad modum* Billroth I with an 8 8 per cent mortality which was lower than almost any series of cases treated by simple closure at that time Immediate resection was adopted widely on the Continent but in the United States and in Great Britain because of the influence of

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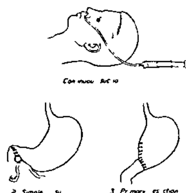



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the amount on a piece of paper she has to take an active step in the matter"

During the period of continuous aspiration a decision can be made as to whether to continue the treatment or whether to perform an operation either simple closure or immediate partial gastrectomy If it is decided to continue treatment by aspiration a second X ray of the abdomen is taken after twelve hours to determine (1) the position of the tube in the stomach (it should be in a dependent portion) (2) the presence of a fluid level in the stomach (there should be none) and (3) an increase in subdiaphragmatic air indicating failure of the fibrin seal of the perforation (either a larger stomach tube is indicated or the perforation should be closed by simple closure)

TABLE 1

RESULTS OF TREATING PERFORATED PEPTIC ULCER BY ASPIRATION OF THE STOMACH

| Follow up Result | Total Number of Follow ups | Acute Ulcer Patients | Chronic Ulcer Patients |
|---|---|---|---|
| *No further symptoms* | 64 | 42 (93%) | 22 (20%) |
| *Subsequent ulcer symptoms* | | | |
| Moderate | 24 | 3 (7%) | 21 (20%) |
| Severe (no operation) | 14 | 0 | 14 (13%) |
| Very severe (later partial gastrectomy) | 48 | 0 | 48 (44%) |
| Died of ulcer | 3 | 0 | 3 (3%) |
| Total | 153 | 45 | 108 |

*Modified from Taylor and Warren 1956*

The results of continuous aspiration when performed in acute cases (Taylor and Warren 1956 Taylor 1957) or in young patients seems to be comparable with the best that other methods have to offer (1–7 per cent mortality) (see Table 1) On the other hand in selected patients too *ill for operation the mortality is high* Martinis Olson and Harkins (1957) report that under these *special* circumstances the mortality of moribund cases given suction treatment varied from 45 5 to 77 4 per cent

*Simple Closure* —This is the stock in trade method used in this country today Recent doubts have been cast upon it from the following three standpoints First the follow up results indicate a higher percentage of serious subsequent morbidity (recurrent ulcer reperforation need for subsequent operation etc ) particularly in chronic ulcers Second simple closure may in some instances convert an acute ulcer into a chronic ulcer Third the immediate postoperative morbidity and related mortality may

actually equal or in some cases even exceed that of definitive resection

*Definitive early subtotal gastric resection*—This method has the advantages of low immediate postoperative morbidity and operative mortality Because most perforations are anterior it is often easier to do a resection for perforated duodenal ulcer than for other indications Most certainly the remote morbidity is less in those cases which would otherwise reperforate etc The big question about immediate resection is how one can avoid resecting a perforated ulcer that would never have caused the patient further trouble if the aspiration or simple closure methods had been utilized instead In the average private hospital series this important question would apply to 30–40 per cent of the patients in the average county hospital series to possibly 20 per cent The most promising lead in this direction has been furnished by Jones and Doll (1953) and by Taylor and Warren (1956) Considering subsequent gastric operation as a minimal indication of serious morbidity following simple closure Jones and Doll reported 18 per cent in the acute cases (defined by them as having a history of dyspepsia of less than twelve months duration) and 41 per cent in the chronic cases with a history of dyspepsia of more than twelve months duration Taylor and Warren s results of the aspiration method using three months history as the differentiating point between acute and chronic cases showed respective incidences of 0 and 44 per cent of subsequent partial gastrectomy (see Table 1)

Our over all experience at the King County Hospital involves the treatment by all methods of slightly over 500 patients with perforated peptic ulcer The majority of these perforations were of duodenal ulcer Our experience with early definitive subtotal gastric resection for perforated ulcer (100 cases) indicates certain considerations which must be taken into account before performing the operation including

1 Satisfactory general condition of the patient
2 Consideration of the patient s physiologic rather than chronologic age
3 Absence of bacterial peritonitis (which often depends more on the individual perforation—size location sealing off etc —than on the number of hours since onset)
4 Adequate experience of the operator
5 Adequate help anesthesia and operating and postoperative facilities

If these precautions are observed the operation is then justified by the presence of one or more of the following definite indications

1 Multiple ulcers
2 Callused ulcers
3 Large perforations
4 Fixed pyloric obstruction
5 Gastric ulcers

6 Concomitant or previous hemorrhage
7 Previous perforation
8 Previous diagnosis of ulcer previous demonstration of ulcer or previous history of dyspepsia indicative of ulcer—all of more than three months duration
9 Unreliability on the part of the patient in co operating with a postoperative medical regime for control of his ulcer after simple closure (This indication applies particularly *to those with coincident chronic alcoholism a frequent* combination in our hospital )

Because of uncertainty as to how much danger there would be of mediastinitis if the esophageal hiatus were opened in the presence of perforated ulcer we have not performed vagotomy with our resections Instead we have utilized the usual measured subtotal (70–75 per cent) resection usually *ad modum* Billroth I

On the basis of these observations and experiences a fourfold program for the treatment of perforated duodenal ulcer is proposed

1 Seriously ill patients with peritonitis (approximately 5 per cent of patients in the Taylor series)—simple closure
2 Seriously ill from unrelated disease but with perforation as well (5 per cent)—continuous aspiration
3 *Not seriously ill and with* a rupture of an acute ulcer *absence of previous* history of ulcer symptoms (30 per cent)—continuous aspiration
4 Not seriously ill and with a rupture of a complicated acute ulcer (associated bleeding or pyloric stenosis) or with chronic ulcer complicated or uncomplicated (60 per cent of patients)—immediate subtotal gastric resection

It *is to be noted that the currently most popular method* simple closure has a small role in this plan While only the future can judge with finality the merits of this proposal it is based on sound observations on large series of perforated ulcer wherein the important differentiation between acute and chronic cases is made (Jones and Doll 1953 Taylor 1957 and others) The writers wish to enter a plea that all those who plan future reports on perforated ulcer series similarly differentiate between acute and chronic cases

Table 1 indicates the great disparities following continuous aspiration in ulcer cases classified as acute or chronic at the time of perforation The percentage that remained well was 93 per cent in the acute cases and only 20 per cent when the ulcer was chronic Similarly there were moderate or severe symptoms in only 7 per cent of the acute cases and in 80 per cent of the chronic cases None of the acute cases led to subsequent partial gastrectomy while 48 (44 per cent) of the chronic cases had such severe subsequent symptoms that a partial gastrectomy was required later These observations would indicate that the ultimate results are excellent in acute ulcers that perforate when continuous aspiration is used as the definitive

treatment Since the mortality with this treatment for such cases is recognized as being low it would seem logical to conclude that if one has a patient with a history of less than three months duration without massive pneumoperitoneum and without relapse in the hospital it is safe and preferable to utilize continuous aspiration Under most other circumstances early definitive resection is indicated

## MASSIVE HEMORRHAGE

Recurrent minor hemorrhages represent an indication for operation under the heading of intractability of the ulcer rather than of hemorrhage per se Massive hemorrhage from a duodenal ulcer presents many problems which are still unsolved Whether the diagnosis is certain or uncertain the

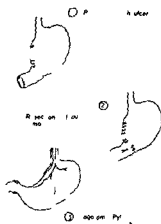


Fig 3 —Surgical treatment of massive hemorrhage from peptic ulcer

surgeon must decide the wisdom of operation and the timing Suffice it to say that if the diagnosis is uncertain we exhaust every diagnostic means possible before performing a blind resection This method introduced by Wangensteen (1945) is often the best thing to do under the circumstances but it still has an element of finality to the patient even if he survives and it is seldom satisfying to the surgeon

The question as to which procedure (Fig 3) is preferable when the diagnosis is certain also presents many difficulties Karlson Enquist Dennis and Fierst (1958) attempted to compare on a preselected rotation basis the results from three methods (1) ultraconservative (Andresen) (2) aggressive surgical (Stewart) and (3) selective The results in a small group of cases indicated that the ultraconservative method did as well as or better than the other two as far as mortality is concerned On the other hand in some instances operation will save a patient and it is

a difficult decision to permit a patient who is bleeding to bleed to death As Dunphy (1958) stated until more data are available "I think we should regard bleeding ulcer in general as an exsanguination syndrome best treated in the selected patient by operation

Finally in our experience even the use of balloon tubes has not completely eliminated the frequent danger of aspiration pneumonia in massive upper gastrointestinal tract bleeding Wangensteen (1958) pointed out that massive hemorrhage is the most frequent cause of death in peptic ulcer This complication is the current unsolved problem in peptic ulcer

## SUMMARY

In this chapter we have discussed the indications for operation in duodenal ulcer These indications include obstruction intractability and incompatibility of medical treatment Certain physiologic studies have been listed which were carried out during the past few years We have pointed out that while twenty years ago there was only one acceptable operation for duodenal ulcer (gastric resection *ad modum* Billroth II) and ten years ago only two such operations (gastric resection *ad modum* Billroth II or vagotomy plus drainage procedure) today there are many apparently good operations for complicated duodenal ulcer Any decision as to a preference rating of these procedures must be based on physiologic studies as well as on clinical experience

The treatment of perforated duodenal ulcer is accompanied by an ever lower mortality using any of three methods of treatment currently in vogue—continuous aspiration simple closure and early subtotal gastric resection *It would seem that consideration should be given to a wider* use of the suction method in acute ulcers (those with a history of dyspepsia or evidence of ulcer of less than three months duration) Similarly resection should be used in more cases of truly chronic ulcer Simple closure would then be utilized for a smaller group of intermediate cases and would not be performed as frequently as it now is in most clinics

The best treatment of massive hemorrhage from duodenal ulcer is even more uncertain at present Unlike the situation with duodenal ulcer in general or with perforated duodenal ulcer where we have not only raised questions but have ventured to answer them in the case of massive hemorrhage we can only raise the questions It is hoped that future studies will help answer this unsolved problem in duodenal ulcer management

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strengthened the belief that some form of gastric drainage should become a part of vagotomy since vagotomy retarded gastric motility thereby[1] favoring stasis Gastric stasis was observed in spite of little or no stenosis at the ulcer site

GASTROENTEROSTOMY IN RELATION TO GASTRIC STASIS

Gastroenterostomy thus became routine for all patients when vagotomy was the surgical treatment performed In some patients it was more convenient to place the gastroenterostomy somewhat higher on the greater curvature than was the usual case Experience soon demonstrated that a high lying gastroenterostomy failed to provide adequate drainage of the stomach This was in part the result of hypomotility after vagotomy partly due to the scarring and contracture of the lumen when present The retained gastric contents in these patients served to distend the antrum and thereby activate the gastrin mechanism causing hypersecretion of gastric juice Thus a patient in whom the original ulcer was of cephalic origin might again become prey to hypersecretion this time from the antrum Curiously recurrence of the previous duodenal ulcer was rarely observed More commonly ulceration occurred in a new location

Dr William E Adams who with Dr Dallas B Phemister performed the first successful primary anastomosis of the lower esophagus and upper stomach for carcinoma of the esophagus (1937) realized that bilateral vagotomy could not be avoided in esophagogastric resections for malignant disease This suggested that gastric ulcer might be a complication of such resections in which pyloroplasty or gastroenterostomy had not been performed during the earlier years of this procedure Gastric ulcer as a complication had occurred in four patients of the group when neither pyloroplasty nor gastroenterostomy had been performed (chap 4)

The problem of gastric stasis was further pursued experimentally by Dragstedt s group at Chicago Many of these experiments have been discussed by Dr Oberhelman in chapter 4 The essential conclusion from these experiments was that gastroenterostomy placed sufficiently low in the stomach to permit complete drainage after vagotomy should prevent antral stimulation

HYPERSECRETION FOLLOWING VAGOTOMY

Neither clinical nor experimental observation explained why the ulcer after complete vagotomy should occur at the stomal site rather than in the duodenum In fact when taking into account only the concentration of free acid in the gastric content it did not seem possible to explain why these patients would develop either a stomal or a duodenal ulcer They were readmitted for further study In some the concentration did prove to

STANLEY P RIGLER

# 8 *Clinical Importance of the Cephalic Secretory Phase Results of Vagotomy and Gastroenterostomy*

During the past fifteen years at least five types of surgical operations have been employed in the treatment of duodenal ulcer Some of these have been discussed in the preceding chapter by Dr Harkins There is no agreement as to which operation is best and it is probably better that no one operation dominate the surgical theater in the treatment of duodenal ulcer In the first place the vagaries of anatomic detail as well as changes secondary to the ulcer itself will necessitate occasional modifications of otherwise standardized procedures As further physiological information becomes available and is applicable to the pathogenesis of ulcer it may be possible to devise more physiologically valid operations or at least to select more wisely that procedure which is best suited to the particular patient Finally a surgeon s individual background and experience will always play an important role in his choosing one procedure for use when other considerations do not weigh heavily in his decision

## THE EVOLUTION OF VAGOTOMY

Fundamental to an understanding of the data on vagotomy is an awareness that this surgical technic has been modified from time to time as experience has accumulated When Dragstedt introduced the operation in 1943 the first objective was to evaluate the effect of vagotomy alone on duodenal ulcer Therefore in the absence of gastric retention from scarring in the region of the duodenal ulcer vagotomy was performed without gastroenterostomy or pyloroplasty In all vagotomy is the only operative procedure was performed on 161 patients Gastric acidity after vagotomy was reduced to levels below normal and the ulcers healed But this series

in most patients and generally disappear after a few months to a year even when no drainage procedure is included

## VAGOTOMY AS THE OPERATION OF CHOICE

At the University of Chicago Clinics vagotomy remains the treatment of choice for most patients with duodenal ulcer The exceptions are patients who are bleeding massively at the time of operation or who have duodenal perforations Excision of the ulcer and ligation of its blood supply or closure of the perforation seem absolutely essential under these circumstances Generally these maneuvers are best accomplished with some form of gastric resection although the local excision of the ulcer with ligation of the bleeding artery fore and aft as suggested by Weinberg has been used successfully here in some patients In the case of perforation simple closure is adequate

### POSTOPERATIVE MANAGEMENT OF PATIENTS WITH VAGOTOMY

Gastric retention during the early postoperative period continues as a potential problem When it occurs it is a disturbing complication but we are convinced that careful adherence to rigid principles of management will prevent nearly all such problems It must be emphasized again that the stomach after vagotomy is remarkably susceptible to acute gastric dilatation and that once this develops it is difficult to treat The vagotomized stomach tolerates distention poorly and does not recover rapidly if distention is allowed to develop However it will seldom occur if the following principles are followed

1 Maintenance of decompression by nasogastric tube or gastrostomy tube for at least the first four postoperative days
2 On the fifth sixth seventh and eighth postoperative days clear liquids only are allowed commencing with 30 ml in increments of 30 ml each hour each day until a total of 120 ml is being well tolerated
3 The stomach should be aspirated approximately two hours after the final feeding each night for several days once the patient begins to eat If the residual is more than 150 ml the feeding should not be increased for a few days
4 During successive days the diet progresses from full liquid to soft but always in small amounts per feeding Frequent small feedings but of adequate caloric composition should be the rule for four to six weeks following vagotomy At the end of this time all dietary restrictions are removed although as with any patient discretion is recommended

In our experience adherence to this program has eliminated nearly all the problems of gastric retention during the immediate postoperative period

be increased but the **quantity** of free acid produced was above normal in all instances The real culprit—an increased output of hydrochloric acid—*was masked when only concentration of hydrochloric acid was taken into* account

Three explanations for the hypersecretion seemed plausible if vagotomy was complete First usually vagotomy does not abolish completely the secretion of free hydrochloric acid as the antral phase of secretion remains intact Second with gastric retention acid accumulates and bathes the gastric mucosa continuously in contrast to the more or less cyclic phase of gastric secretion normally observed Third with gastric retention *the resultant distention of the antrum augments the function of the gastrin* mechanism Of the three the most important is probably the continual bathing of the gastric mucosa by free hydrochloric acid Otherwise one would expect that duodenal ulcer would be the natural sequela

THE DUMPING SYNDROME

Another of the earlier complications of vagotomy was the **dumping syndrome**—certainly not new to the surgery of duodenal ulcer In fact dumping had become sufficiently common in several centers to be considered essentially an unavoidable consequence of resection and it was not being taken into account in the appraisal of end results In recent years more attention has been given to the disabling effect of dumping following gastric resection and it is included among the more important unfavorable sequelae of all forms of gastric surgery The dumping syndrome is also a complication of gastroenterostomy alone it was seen when this was the procedure used for the surgical treatment of peptic ulcer Dumping may also be observed following pyloroplasty

Randall and his associates recently demonstrated that there is a marked decrease in blood volume following the rapid entrance of hypertonic solution into the small bowel drawing heavily upon plasma water and its electrolyte components This hypotension like state appears to explain many of the symptoms referable to the dumping syndrome However two or three hours later severe hypoglycemia may develop and this in turn may produce a clinical pattern similar to that of an insulin reaction

Belching and diarrhea were also frequent and distressing complications *of vagotomy particularly when vagotomy was performed without a* drainage procedure These symptoms have been attributed to fermentation of retained food Following the use of gastroenterostomy there has been a pronounced diminution of the seriousness of these complaints However careful questioning of patients reveals that these remain the symptoms which more than other complications follow vagotomy and gastroenterostomy Fortunately these two complaints gradually diminish

ation provides only a partial understanding of the problem presented by the operated patient On the other hand highly subjective variables such as the patient s assessment of his benefits are subject to serious misinterpretation Thus the terms one uses to describe his results become of paramount importance The following definitions of results have been employed in an attempt to evaluate these patients as objectively as possible

**Excellent**—the patient is completely free of gastrointestinal symptoms of any kind without need for medication or dietary restriction

**Good**—the patient is completely free of ulcer symptoms but has minor and infrequent gastrointestinal symptoms which may well be functional and which require only simple or sporadic dietary regulation

**Fair**—the patient is completely free of ulcer symptoms but is troubled by gastrointestinal disturbances which are incompletely controlled by diet or medication symptoms do not interfere with his social or vocational activities

**Poor**—this category includes operative deaths recurrences and disabling nutritional or gastrointestinal symptoms

**Operative deaths** are defined as those occurring within thirty days of the day of surgery **Recurrence** means postoperative ulceration—duodenal marginal or gastric—preferably but not necessarily proved by X ray or re exploration We have not employed the distinction between **proved** and **possible** recurrence The presence of symptoms suggestive of a recurrence has the same significance for the patient and his future whether or not recurrence is proved conclusively Occurrence postoperatively of typical ulcer symptoms or symptoms similar to those present preoperatively is considered presumptive evidence of recurrence Gastrointestinal hemorrhage of any magnitude or form is considered indicative of recurrent ulceration

We and others have been impressed by a syndrome occurring after vagotomy which includes **epigastric distress and melena** although the measured acid secretion is low Several of these patients have exhibited an erosive gastritis at reoperation without any discrete ulcer The physiologic significance of this syndrome is not understood at the present time but these patients are considered to have recurrent ulceration

Included in the group of patients with **nutritional disturbances** are those with the **dumping syndrome** those who have lost a significant amount of weight or who have failed to regain their optimum weight patients with stasis and gastric retention of sufficient degree to require rigid dietary management and a small group with severe and persistent diarrhea

A tabulation of the results of therapy in the 724 patients who could be traced is as follows

## EVALUATION OF VAGOTOMY AND GASTROENTEROSTOMY

Inevitably interest in the ulcer problem leads to concern about methods for reporting results of therapy Granted that duodenal ulcer is a chronic and recurring disease it would seem that standards similar to those used in reporting on cancer would be desirable A parallel to the five year survival rates in cancer patients would be to report results of treatment for duodenal ulcer in terms of freedom from disease after five and ten years or longer A subsequent publication from this laboratory will be devoted to a long term follow up on a group of 500 patients However it seems appropriate at this time to review the total experience at the University of Chicago in the treatment of duodenal ulcer by vagotomy and gastroenterostomy

### COMPOSITION OF THE PATIENT SERIES AT CHICAGO

Between 1943 and 1945 vagotomy alone was the procedure used in the majority of patients a drainage procedure being done only when there was evidence of scarring in the region of the pylorus A total of 161 patients had transthoracic or transabdominal vagotomy without associated gastroenterostomy The recurrence rate in this group of patients was comparable to those treated by the combined operation However as has been indicated above a significant number had distressing symptoms of gastric retention necessitating a subsequent gastroenterostomy After 1949 vagotomy was always combined with a gastric drainage procedure For this reason these first 161 patients will not be considered further

Vagotomy plus gastroenterostomy has been performed in 757 patients The indications for operation conformed to the classical tetrad with one exception operation was occasionally recommended for patients with nocturnal secretions six to eight times in excess of normal in spite of the absence of classical indications for surgical intervention In general vagotomy was not performed on patients who were bleeding massively at the time of operation However hemorrhage which had ceased several days prior to operation was not considered a contraindication to vagotomy

Follow up has been achieved in 95 per cent or 724 patients Wherever practical follow up information was obtained by personal interview and appropriate diagnostic studies When this approach failed use was made of a questionnaire which has proven to be a reliable estimate of the patient s situation Patients have been followed from 1 to 15 years

### REPORTING THE RESULTS

In the treatment of duodenal ulcer evaluation of the results of therapy is difficult at best Consideration of such quantifiable modalities as change in weight return to former occupation and freedom from recurrent ulcer

ation provides only a partial understanding of the problem presented by the operated patient. On the other hand, highly subjective variables such as the patient's assessment of his benefits are subject to serious misinterpretation. Thus the terms one uses to describe his results become of paramount importance. The following definitions of results have been employed in an attempt to evaluate these patients as objectively as possible:

**Excellent**—the patient is completely free of gastrointestinal symptoms of any kind, without need for medication or dietary restriction.
**Good**—the patient is completely free of ulcer symptoms but has minor and infrequent gastrointestinal symptoms, which may well be functional and which require only simple or sporadic dietary regulation.
**Fair**—the patient is completely free of ulcer symptoms but is troubled by gastrointestinal disturbances which are incompletely controlled by diet or medication; symptoms do not interfere with his social or vocational activities.
**Poor**—this category includes operative deaths, recurrences, and disabling nutritional or gastrointestinal symptoms.

**Operative deaths** are defined as those occurring within thirty days of the day of surgery. **Recurrence** means postoperative ulceration—duodenal, marginal or gastric—preferably but not necessarily proved by X-ray or re-exploration. We have not employed the distinction between **proved and possible** recurrence. The presence of symptoms suggestive of a recurrence has the same significance for the patient and his future whether or not recurrence is proved conclusively. Occurrence postoperatively of typical ulcer symptoms, or symptoms similar to those present preoperatively, is considered presumptive evidence of recurrence. Gastrointestinal hemorrhage of any magnitude or form is considered indicative of recurrent ulceration.

We and others have been impressed by a syndrome occurring after vagotomy which includes **epigastric distress and melena** although the measured acid secretion is low. Several of these patients have exhibited an erosive gastritis at reoperation without any discrete ulcer. The physiologic significance of this syndrome is not understood at the present time, but these patients are considered to have recurrent ulceration.

Included in the group of patients with **nutritional disturbances** are those with the **dumping syndrome**, those who have lost a significant amount of weight or who have failed to regain their optimum weight, patients with stasis and gastric retention of sufficient degree to require rigid dietary management, and a small group with severe and persistent diarrhea.

A tabulation of the results of therapy in the 724 patients who could be traced is as follows:

| | |
|---|---|
| Excellent results | 378 patients (52 per cent) |
| Good results | 195 patients (27 per cent) |
| Fair results | 51 patients ( 7 per cent) |
| Poor results | 100 patients (14 per cent) |

An analysis of the **poor results** shows that there were eight operative deaths an operative mortality of 1 per cent These deaths were due to bronchopneumonia cerebral vascular accident and myocardial infarction There was in addition one death attributable to peritonitis following breakdown of the gastroenterostomy

The 92 surviving patients who are rated as showing poor results may be listed according to the site of their recurring ulcer or the nature of their nutritional disturbance as follows

| | |
|---|---|
| *Recurrent ulceration* | 77 patients (10 6 per cent) |
| Duodenal ulcer | 8 patients |
| Marginal ulcer | 42 patients |
| Gastric ulcer | 4 patients |
| Erosive gastritis | 23 patients |
| *Gastrointestinal disturbances* | 15 patients (2 per cent) |
| Dumping syndrome | 3 patients |
| Gastric retention | 8 patients |
| Weight loss | 2 patients |
| Diarrhea | 2 patients |

The fate of the 77 patients with recurrent ulceration may be divided into three categories (1) medical management led to relief of symptoms in 43 patients (2) an additional 19 were successfully treated by radiation to the fundus of the stomach and (3) fifteen required subsequent gastric resection This latter group comprises 19 per cent of those patients with recurrence and a little over 2 per cent of the entire series of patients treated by vagotomy and gastroenterostomy

## CONCLUSIONS

In attempting to evaluate an operative procedure for the relief of duodenal ulcer the two questions which are raised most frequently are What is the recurrence rate? And what degree of patient disability may be expected in order to achieve freedom from postoperative complications?

The recurrence rate in this series of 724 patients treated by vagotomy and gastroenterostomy was 10 6 per cent The literature on the results of subtotal gastrectomy show recurrence rates as low as 2–3 per cent and as high as 9 per cent However on the whole we conclude that our incidence of recurrence is somewhat higher than is reported for those series which feature more drastic surgery

As to the second question our operative mortality of 1 per cent is probably irreducible it is certainly lower than that accompanying subtotal gastric resection It is obvious that the disabling effect upon the patient will be less with our minimal operative procedures

As in any evaluation of a medical treatment we are faced with many unknowns—what happened to those patients who could not be traced those who died as a result of operation—and we must keep in mind the objectivity circumspection and accuracy required in assessing the results Reports continue to appear in which the actual conditions are so inadequately described in which the time factors units of measurement and other terms are so loosely defined that comparisons cannot be made between the different methods of treatment Clinical results which cannot be readily appraised by others confuse rather than clarify the ulcer problem We realize that this brief report is not above these criticisms but serious attempts are under way to reduce such deficiencies so that a better accounting may be made of this method of treating duodenal ulcer

Although the figures will change with more subjects and with better reporting of results and comparative studies will perhaps become possible the absolute values of vagotomy are not likely to change Dr Dragstedt summarized these a few years ago in considering the lot of any group of duodenal ulcer patients subjected to vagotomy and gastroenterostomy An unfortunate few he said will develop recurrent ulceration and will be forced to adhere to rigid medical therapy or risk further operations Their position will be but little worse than if they had had resection initially But the great majority of those treated by vagotomy will survive the operation never more to be troubled by their ulcer but retaining a comfortable and efficient gastrointestinal tract

This seems to us a reasonable approach Unfettered by the feeling that an ulcerless patient is a well patient yet not compromised by the concept that an intact digestive system is its own reward the surgeon with this attitude can attack ulcer disease with considerable hope of success coupled with the knowledge that the people he labors to help will be no more handicapped than before he met them

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JOSEPH B KIRSNER
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# 9 *Gastric Ulcer Peptic Activity in the Physiology, Pathology, Clinical Course, and Therapy*

The purpose of this paper is to discuss the role of free hydrochloric acid and peptic digestion in gastric ulcer Its pathogenesis and course and the mechanism of pain are directly related to peptic activity The problem in differential diagnosis arises from peptic digestion in cancer The basic principles of therapy relate to the control of the acid pepsin factor Our concepts will be introduced by the presentation of four selected cases

**Case 1**—G M a fifty eight year old white male admitted on May 22 1955 *gave a history for the previous five months of intense gnawing postprandial* epigastric pain partially relieved by milk He had lost five pounds A large ulcer near the cardia of the stomach had been reported by radiologic examination elsewhere and treatment had been instituted with symptomatic relief An active duodenal ulcer had been diagnosed in 1950

Routine examinations of the blood and urine were normal The stools were negative for occult blood Gastric analysis disclosed a low basal secretion with a maximum rise to fourteen clinical units after the administration of Histalog (Table 1) The gastroscopist did not visualize a lesion Gastric cytologic studies revealed no malignant cells On May 23 and again on August 3 a shallow ulcer crater demonstrated radiologically high on the posterior wall of the lesser curvature was interpreted as benign The patient after discharge from the hospital continued free of pain on strict ulcer management

On November 12 the X ray examiner reported a small posterior gastric ulcer

which was interpreted as a "possible neoplasm On December 3 another examiner described a small ulcer on the greater curvature high in the fundus with unexplained polypoid deformities and stated "Carcinoma is a good possibility "

As will be seen from Figures 1 and 2 the different descriptions all refer to the same ulcer

The patient was readmitted to the hospital on December 14 1955 with no remarkable findings on physical or laboratory examination Eight stools were negative for occult blood The gastric secretory studies were repeated (see Table 1) Cytologic studies were again negative for malignant cells An ulcer 1–2 cm

TABLE 1

GASTRIC ANALYSIS OF CASE 1—C M
(Fasting and Post Histalog Secretion of Free HCl )

| | 1955 | | | 1956 | | | | | | | 1957 | 1958 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 23 | 8 12 | 12 16 | 1 7 | 1 14 | 2 4 | 5 19 | 7 2 | 9 29 | 12 8 | 1 30 | 2 28 |
| Residuum | 0 | 0 | 0 | X ray therapy completed | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Basal* | | | | | | | | | | | | |
| 15 min | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 min | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 min | 4 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 min | Trace | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Histalog* | | | | | | | | | | | | |
| 15 min | 2 | 12 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 min | 14 | 23 | 15 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 45 min | 12 | 17 | 19 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 min | 14 | 28 | [illegible]8 | | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total Mg HCl | 47 | 103 | 82 | | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total mEq HCl | 1 3 | 2 9 | [illegible] 2 | | 0 03 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Fo t h (42)

in diameter located just below the cardia was visualized incompletely at gastroscopy malignancy could not be excluded X ray examination of the stomach on December 17 reported a "marked increase in the size of the ulcer high on the posterior wall near the fundus—cannot rule out carcinoma "

The pain had become severe and was continuous day and night Strict ulcer management with an anticholinergic drug and hourly doses (4 0 gm ) of calcium carbonate and 90 cc of equal parts of milk and cream failed to afford relief for several days finally constant gastric suction relieved the pain Day and night milk and antacid therapy was then resumed Roentgen irradiation (1 600 r) to the fundus and body of the stomach was instituted on January 6 1956 to produce achlorhydria if possible Roentgenologic examination at the end of therapy on January 17 1956 demonstrated an enormous 2 0 × 2 5 cm crater on the posterior wall of the fundus looking like a diverticulum

All subsequent gastric analyses failed to elicit free acid X ray examination on January 31 demonstrated a decrease in the size of the ulcer Gastroscopic examination on February 5 disclosed an ulcer estimated to be 1 0 cm in diameter and interpreted as definitely benign The patient continued free of pain and was discharged February 9 1956 on a strict ulcer management Roentgenologic examinations of the stomach in March and August 1956 January 1957 and March 1958 demonstrated no abnormality (Fig 3) Repeated fecal examinations were negative for occult blood The gastroscopic examination and the cytologic study were again negative in January 1957 In March 1958 the patient reported that he had had no recurrence of epigastric pain On April 17 1958 he died of a cerebrovascular thrombosis as shown by autopsy A well healed fibrotic scar was found in the stomach at the site of the old ulcer (Fig 4)

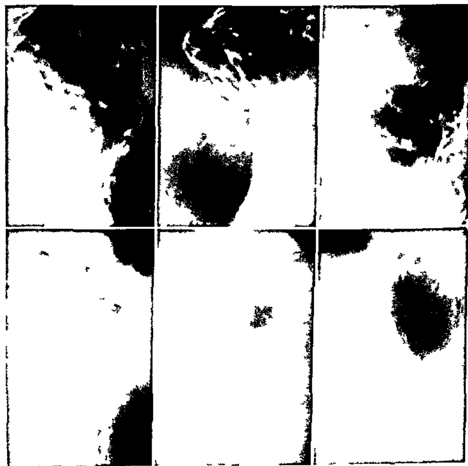


FIG 1 —*Case 1* Small gastric ulcer located on the posterior wall high in the stomach increasing in size from May to August to November (*three top views*) to December (*three lower views*) The three lower views (December 3 1955) show the ulcer *en face* and *en profile* lesser curvature

**Case 2**—D M a white female was twenty nine years of age when first seen in 1954 for nausea of eight days duration She weighed 105 pounds was 5 ft 7 in tall and tense and nervous in temperament A complete gastrointestinal examination including X ray studies and gastric cytology was negative Gastroscopic examination disclosed minimal patchy atrophic gastritis The gastric analysis revealed a low basal secretion with a peak of 49 clinical units after the injection of Histalog (Table 2)

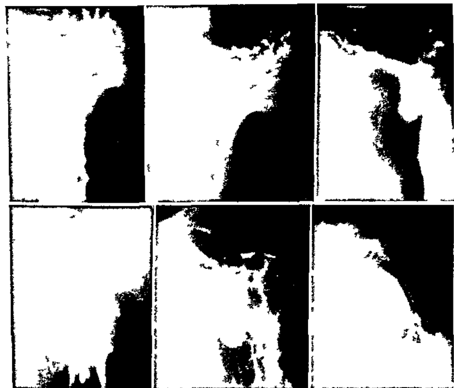


FIG 2—*Case I* Further increase in the size of the ulcer shown in Fig 1 The differing appearance of the lesion in different projections is apparent in the three top exposures of December 17 and also in the three bottom exposures of January 17 1956 The greater size and depth of the ulcer compared with the earlier views is apparent and in our judgment can only be ascribed to an increase in the size of the original ulcer

In January 1955 she developed nausea after eating plus pain located high in the epigastrium and she was hospitalized on February 2 The physical and laboratory examinations were not remarkable except for a four plus reaction for occult blood in the feces by the benzidine test Gastroduodenal X ray examination demonstrated an ulcer 2 0 cm in diameter and 1 5 cm in depth on the lower part of the lesser curvature it was judged almost certainly benign (Fig 5) Gastroscopy revealed an ulcer approximately 1 5 cm in diameter and 0 5

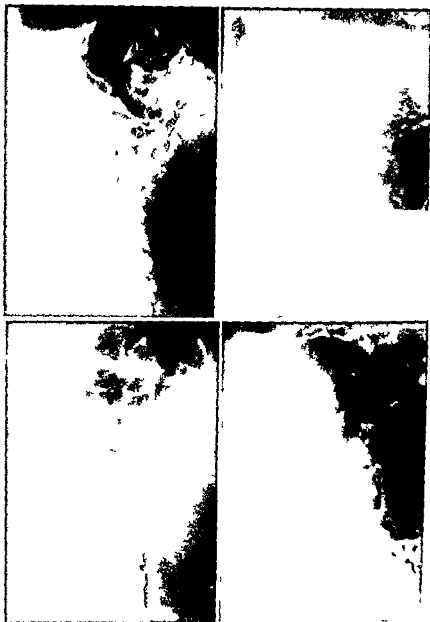


Fig 3 —*Case 1* Healing of the ulcer with normal mucosal pattern *Upper left* March 1956 *upper right* August 1956 *lower left* January 1957 *lower right* March 1958



Fig 4 — *Case 1* Note integrity of mucosa with absence of underlying submucosa and muscularis at site of previous ulcer

TABLE 2

Gastric Analysis of Case 2—D M
(Fasting and Post Histalog Secretion of Free HCl)

| | 1954 | 1955 | | | | | | | | 1956 | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 3 4 | 2 8 | 3 4 | 3 7 | 3 21 | 4 12 | 4 28 | 5 20 | 9 13 | 1 3 | 10–22 |
| Residuum | 4 | 0 | X ray therapy completed | 0 | 6 | 0 | 0 | 16 | 9 | 0 | 0 |
| *Basal* | | | | | | | | | | | |
| 15 min | 0 | 0 | | 18 | 34 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 min | 0 | 0 | | 51 | 46 | 0 | 0 | Trace | 0 | 0 | 0 |
| 45 min | 0 | 0 | | 59 | 49 | 0 | 0 | 0 | 0 | 0 | 0 |
| 60 min | 0 | 0 | | 60 | 96 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Histalog* | | | | | | | | | | | |
| 15 min | 0 | 0 | | 75 | 34 | 0 | 0 | 0 | 0 | 0 | 0 |
| 30 min | 10 | 46 | | 81 | 64 | 1 | 0 | 0 | 0 | 0 | 33 |
| 45 min | 49 | 91 | | 79 | 75 | 20 | 0 | 0 | 0 | 0 | 45 |
| 60 min | 46 | 85 | | 68 | 65 | 19 | 0 | 0 | 0 | 0 | 44 |
| Total Mg HCl | 112 | 282 | | 791 | 277 | 25 | 0 | 0 | 0 | 0 | 78 |
| Total mEq HCl | 3 1 | 7 7 | | 21 7 | 7 6 | 0 7 | 0 | 0 | 0 | 0 | 2 1 |

cm deep just proximal to the angulus Peristalsis was normal the margin of the ulcer was sharply demarcated it was called probably benign Calcium carbonate (2 0 gm ) alternating with 90 cc half milk and half cream every half hour were prescribed Pamine was given in daily doses increasing from 5 0 mg to 32 5 mg the larger dose administered continuously from March 18 to May 12 The milk and calcium carbonate were continued every two hours throughout the

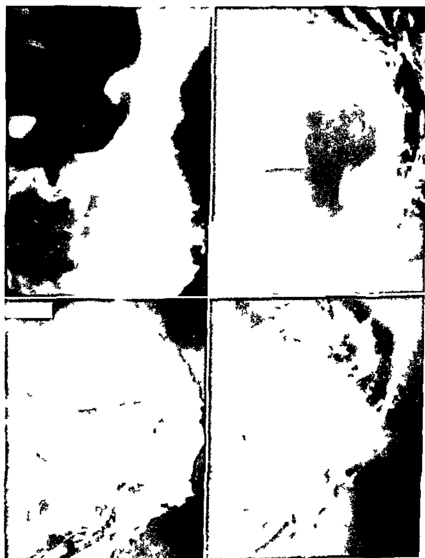


FIG 5 —*Case 2* Healing of a large ulcer of the lesser curvature with restoration of a normal mucosal fold pattern *Top views* February–March 1955 *lower left* April 1955 *lower right* January 1957

night the pain persisted On March 23 the patient was given a constant intra gastric drip containing 10 gm sodium bicarbonate per liter of milk which pro vided complete relief The patient received gastric radiation therapy (1 650 r) beginning February 21 and ending March 3 (See Table 2 for the subsequent gastric analyses ) The intragastric drip was discontinued on April 7 and the patient remained symptom free Gastric cytology prior to discharge was again negative On April 8 1955 gastroduodenal films showed only a very shallow scar pocket remaining at the site of the previously demonstrated crater Five subsequent examinations to January 1958 have all disclosed a normal stomach (see Fig 5) The patient has continued antacid medication Pamine and pheno barbital with no return of symptoms

**Case 3**—**J C** a white male was first seen in July 1938 at the age of forty with a history of postprandial and nocturnal epigastric pain for two years A duo denal ulcer was said to have been demonstrated in May 1937 The advice of hospitalization had not been accepted Periodic episodes of pain continued but the patient was symptom free whenever he adhered to a rigorous medical pro gram In 1943 following a recurrence of pain he had X ray films taken which were said to have revealed a gastric ulcer In 1944 he experienced hematemesis and was advised elsewhere that immediate surgery was mandatory He then re turned for our advice

The histamine test revealed a peak of 85 clinical units of hydrochloric acid X ray examination demonstrated an ulcer crater on the lesser curvature of the stomach (Fig 6) The initial gastroscopic examination disclosed an ulcer about 2 0 cm in diameter which could not be differentiated completely from a malig nant ulcer However two weeks later on December 18 the ulcer had decreased in size as seen gastroscopically and radiologically it appeared benign On January 5 1945 the ulcer gastroscopically was smaller and shallower the borders were sharp and clean cut there was no nodularity or stiffness the surrounding mucosa appeared soft and pliable the appearance was that of a healing benign ulcer Examination of the stools for occult blood varied from negative to a faintly positive reaction

Treatment consisted of the standard antacid program in the hospital from No vember 22 1944 to January 9 1945 Roentgen irradiation (1 600 r) was directed to the fundus and body of the stomach over a sixteen day period ending January 6 and resulted in a histamine fast achlorhydria On May 9 1945 roentgenograms disclosed the gastric ulcer to be healed and the mucosal pattern normal Gastro scopic examination noted the slow but progressive healing of the ulcer on Febru ary 5 and March 14 with complete healing by April 4 1945 Subsequent gastro scopic examinations in October 1945 January 1948 and November 1949 re vealed a normal mucosa except for patchy areas of atrophy Subsequent X ray examinations the last in March 1951 demonstrated the duodenal deformity and the normal stomach (Fig 7) Histamine fast achlorhydria was still present An nual reports by mail to October 1957 indicate that the patient has had no sub sequent distress

**Case 4**—A K, a white female, was sixty three years old when first seen in April 1936 She had had periodic epigastric distress of the ulcer type for thirty years Roentgenologic examination disclosed an ulcer benign in appearance high on the lesser curvature of the stomach Gastroscopically the lesion appeared benign Treatment with milk antacids and diet was followed by a remission of symptoms X rays in May and July indicated healing with scar formation but in October an ulcer again was demonstrated on the posterior wall of the lesser curvature Gastroscopic examinations totaling well over one hundred permitted




Fig 6—*Case 3* Duodenal and gastric ulcer (*A* and *B* January 1945) with complete healing and restoration of the mucosal pattern (*C* 1948 and *D* 1951)

continued observation of the ulcer as it fluctuated in size healed and recurred The symptoms waxed and waned as the patient adhered more or less faithfully to treatment In April 1946 with a recurrence of symptoms and with demonstration of the lesion again gastroscopically and radiologically at the same spot in the stomach as on previous occasions she was given 1 600 r to the body and fundus of the stomach The ulcer healed and has remained healed to date (March 1958) as shown by lack of symptoms and by repeated gastroscopic and roentgenologic examinations The achlorhydria has also persisted (Fig 8) The patient now eighty five years of age continues in excellent health

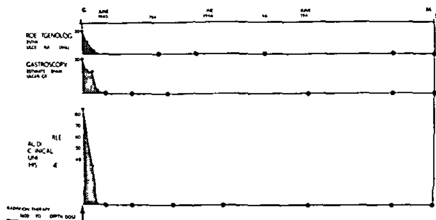



FIG 7—*Case 3* Clinical course indicating healing of the ulcer and achlorhydria present to March 1951 graphically portrayed in terms of radiology (Fig 6) gastroscopy and gastric analysis

## PATHOGENESIS

### PENETRATION VERSUS INFARCTION

Pathologists formerly favored the theory that peptic ulcer arose from an **infarct,** because of the gross appearance of the lesion at autopsy and because they found thrombosed vessels in the base Subsequent workers attributed the thrombosis to the inflammatory process (1) That the lesion is in fact **penetrative** is evidenced by a number of facts The clinical features themselves are suggestive—recurrence of the ulcer at the same site acute perforation and massive hemorrhage occurring as episodes in the course of a chronic ulcer and indeed the very chronicity of the lesion Experimentally produced ulcers simulating the human lesion are penetrating and lead to death of the animal from acute perforation or massive hemorrhage (2) Localized infarction cannot be produced experimentally by ligation of single arteries because of the abundant collateral circulation The concept of infarction has persisted clinically in spite of these considerations owing largely to the fact that the radiologist

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Fig 6—*Case 3* Duodenal and gastric ulcers (A and B January 1945) with complete healing and restoration of the mucosal pattern (*C* 1948 and *D* 1951)

PEPTIC DIGESTION AND ACID ATTACK VERSUS MUCOSAL RESISTANCE

Hunter's (4) question—Why does not the normal stomach digest itself?—has never been answered fully. The mucous barrier, according to Hollander (5), consists of a layer or sheet of viscous mucus and an underlying layer of tall columnar cells. If this layer of mucus is wiped away continuously for a few minutes under experimental conditions and the surface is bathed in acid gastric juice, an ulcer develops quickly (6, 7). The mucous barrier may be influenced experimentally (45) but not clinically. It is evident that some factor must facilitate the acid-pepsin penetration. A variety of conditions such as edema, anemia, shock, vasoconstriction, and hemoconcentration (23, 24, 25) may increase local vulnerability. Atrophic gastritis is found gastroscopically in 26 per cent of the patients with gastric ulcer, whereas in those with duodenal ulcer it is found in only 5 per cent (26). In the present state of our knowledge, primary emphasis must be placed upon the presence of acid gastric juice, for it is the *sine qua non* of chronic peptic ulcer; the importance of free hydrochloric acid may be likened to that of an essential catalyst in a chemical reaction without which the end product, chronic ulceration, cannot or does not occur.

SECRETORY LEVELS IN PEPTIC ULCER

Levin *et al.* (8) have shown that the mean fasting twelve-hour secretion of free hydrochloric acid is nearly four times as high in patients with duodenal ulcer (2,242 mg. or 61.6 mEq.) as it is in normal individuals (661 mg. or 18.2 mEq.). In gastric ulcer the mean fasting secretion is below normal (454 mg. or 12.5 mEq.). James and Pickering (9) came to similar conclusions. Ulcers in the terminal antrum and the pyloric channel tend to be accompanied by mean secretory values intermediate between those for gastric and duodenal ulcer (10, 11). There are wide ranges in the secretory levels from patient to patient: in duodenal ulcer, wide ranges in the amount of hypersecretion; in gastric ulcer, wide ranges from hyper- to hyposecretion. Dragstedt *et al.* (12) have shown that the hypersecretion in patients with duodenal ulcer is mediated over the vagus nerves; they postulated that in patients with gastric ulcer the stimulus is largely antral in origin (13, 14). Our concern has been to demonstrate the invariable presence of acid secretion in benign gastric ulcer (15). It will be noted that the patients presented in this paper had low secretory levels, yet free hydrochloric acid was present. The transitory achlorhydria occasionally encountered in patients with chronic gastric ulcer is false achlorhydria with pH ranges of 3.5–7.0 (16). Acute or subacute lesions ascertainable only at gastroscopy have been reported in the absence of free acid (17). Relatively little free acid is required to activate pepsinogen

routinely observes a decrease in the size of the lesion Few radiologists have had the opportunity to study patients under the appropriate conditions to observe an increase in size In a paper (3) published in 1938 numerous roentgenograms were reproduced to provide proof of increasing size of both gastric and duodenal ulcers *Evidence in the form of gastroscopic observations* was also presented showing the increase of certain gastric ulcers whose identity could be determined because of their persistence in certain constant areas The evidence was not acceptable to cer

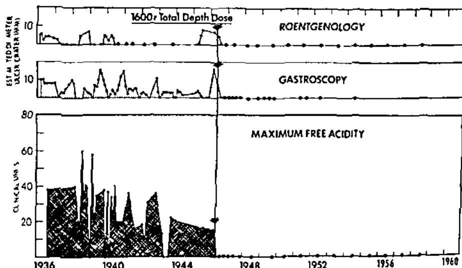



FIG 8—*Case 4* This chart depicts the many X ray and gastroscopic examinations showing the continued presence of a gastric ulcer at a recognizable point in the stomach from 1936 to 1946 The numerous histamine tests rarely showed a maximum free acid secretion above 40 clinical units transitory achlorhydria occurred With the induction of histamine fast achlorhydria in 1946 the ulcer healed and has remained healed to date (April 1958)

tain workers who argued that the apparent increase might be due to different radiologic projections or in fact that the lesions might be different ulcers Additional cases have been observed by us since 1938 but the details have not been published The several photographs selected from the many exposures made in Case 1 are illustrative (Figs 1 and 2) The ulcer increased in size quite dramatically It clearly was the same lesion at all times *it persisted in the same spot on the posterior wall near the cardia* although as the patient was turned from side to side the lesion appeared on the lesser or the greater curvature

Such observations indicate that peptic ulcer is penetrative and not the result of an infarct The question then arises What causes the penetrative process?

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and maintain peptic activity (Fig 9) (18) The role of free hydrochloric acid in pathogenesis is further proved by the fact that when in the course of a chronic gastric ulcer achlorhydria develops or is maintained for a *period of three months or longer* the ulcer heals and does not recur for the duration of the achlorhydria (19) (see Figs 7 and 8)

GASTRIC RETENTION

The association of *gastric retention and gastric ulcer was noted by* Carman in 1917 (20) Emery and Munroe (21) found retention in half of their patients with gastric ulcer Retention provides excessive contact of the mucosa with the acid gastric content The cause of the retention has been related to such conditions as *reflex pylorospasm impaired motility*

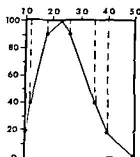



Fig 9—The effect of pH on peptic activity The optimum pH varies depending upon the protein being digested but pepsin approaches 100 per cent efficiency at pH 1 8 2 2 (*After Hollander 18*)

pre existing hypertrophic stenosis of the pylorus pyloric ulcer either healed or active stenosing duodenal ulcer and more recently the post vagotomy state in the absence of an adequate drainage procedure (22)

## THE ORIGIN OF PAIN

The mechanism of pain in peptic ulcer has been elucidated elsewhere (26–30) The evidence indicates that the digestive process resulting in peptic ulcer evokes in the tissue an inflammatory response chemical *in origin* which lowers the pain threshold of the visceral nerves in the edge or base of the ulcer The lowered pH of the gastric content then constitutes an adequate stimulus to the nerve endings The relationship between *the severity of the pain and the concentration of acid is not a direct one* The acidity of the gastric content fluctuates with the rate of secretion the frequency and amount of food eaten the ingestion of antacids and the rate of gastric emptying The inflammatory reaction fluctuates and produces variations in the pain threshold Pain is thus a resultant of the threshold concentration of acid and duration of action Some students of

the problem have found it difficult to understand the presence of pain often severe with relatively low concentrations of acid perhaps they have not appreciated sufficiently the importance of the threshold and the duration of action

In 1946 Bonney and Pickering (31) studied the time required to produce pain with dilute hydrochloric acid in skin ulcers coated with mucus and scab of variable thickness They hypothesized that

> In the skin the pain nerves are almost certainly excited chemically In the stomach all the evidence is in favour of a similar hypothesis It is clear that the time relations of peptic ulcer pain are out of line with the idea that the pain nerve endings lie exposed on the surface of the ulcer they are much too long The time relations are however entirely consistent with the hypothesis that the pain nerves are situated in the floor or sides of the ulcer and separated from the cavity of the stomach by a layer of from this point of view functionally inert material In extending ulcer the slough covering the ulcer base would do for this layer since it is of the expected order of thickness On this hypothesis the pain fibers might arise from many structures such as omentum liver pancreas and posterior abdominal wall which in large chronic ulcers may contribute to the ulcer crater But in acute ulcers the implication is of nerve endings lying in the wall of the stomach itself

The work of Bonney and Pickering is in complete accord with the concept presented

It should be apparent that such nerves with their lowered threshold for the sensation of pain may be stimulated mechanically as well as chemically (28) In a crucial experiment carried out in a patient with a highly sensitive and painful duodenal ulcer subjected to operation under local anesthesia Dragstedt and Palmer (32) produced severe pain by stroking the serosal surface of the ulcer by pinching the ulcer by stimulating the duodenal muscle into contraction and by bathing the surface of the ulcer with a solution of acid The threshold had been lowered so that mechanical or chemical irritation of the lesion evoked severe pain

How does the explanation given fit with the pain observed in the four patients described in this paper? Acid gastric juice was present in all peptic activity was almost surely adequate the milieu was adequate for the production of a chronic gastric ulcer and for the production of pain In patients G M and D M the pain for a number of days was severe and continuous day and night and it was not completely relieved by the ingestion of milk or other food by calcium carbonate in large amounts sodium bicarbonate and an anticholinergic drug in large doses (Pamine 32 5 mg per day) What is the explanation of the failure or at least the difficulty in relieving the pain? It cannot be attributed easily to failure to neutralize temporarily the acid gastric juice or to bring the intragastric pH

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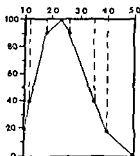



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ing was obtained Dagradi and Johnson (38) in a series of 100 gastric ulcers found three neoplasms (two lymphomas and one carcinoma) The accuracy of the total diagnostic study using the methods now available has thus far been found to approximate or be within the surgical mortality presumably both will improve with refinements in technic How are the various diagnostic criteria to be used and weighed?

### HISTORY AS A DIAGNOSTIC CRITERION

**Chronicity** of symptoms of two years or longer and **periodicity** are infrequent if not rare in gastric cancer unless the patient has suffered from an independent peptic ulcer or dyspeptic complaint Many patients with benign ulcers on the other hand give histories of only a few months duration with no significant remission The distress produced by the two lesions may be identical with the same relationship to the ingestion of food and the same relief from antacids and ulcer management the mechanism of pain is similar

### SYMPTOMS OF LITTLE DIAGNOSTIC VALUE

**Loss of appetite and weight** is not an early feature of the symptomatology of either lesion nor is it obvious in either at a time when differentiation is difficult However it may be fair to say that in general the greater these symptoms are the greater the likelihood of neoplasm

Of little diagnostic value also are **palpable masses** These are late signs of neoplasm whether metastatic or localized

**Anemia** arises from loss of blood except for the non ulcerating neoplasms developing in patients with untreated pernicious anemia hence it is of no differential value

### OCCULT BLOOD IN THE FECES

Although found in both conditions this symptom is important for two reasons Persistently negative stools speak rather strongly for benignancy because at least 75 per cent of gastric cancers bleed persistently On ulcer management benign ulcers should stop bleeding the continued presence of occult blood in the feces is presumptive evidence of malignancy

### GASTRIC ANALYSIS

There is no secretory pattern characteristic of malignancy or benignancy Free acid can always be demonstrated in benign ulcer assuming the use of satisfactory technics including confirmation fluoroscopically of the placement of the tip of the tube in the stomach and utilization of histamine or Histalog Persistent true achlorhydria is incompatible with the diagnosis of benign ulcer Cancer may exist however in the presence of a high secretory pattern

to a high level An explanation frequently offered for such pain is penetration or perforation as though this procedure in itself in some strange way produces pain The pain of an acutely perforated peptic ulcer is attributable to the irritation of the peritoneum by acid gastric juice the acute perforations of other abdominal viscera or of gastric cancers with achlorhydria are not characterized by pain of this type and intensity Furthermore pain of such severity may occur with non perforating ulcer and be relieved invariably by continuous bathing of the surface of the ulcer with buffering duodenal content Thus in patient G M continuous aspiration of the stomach gave relief In D M the same result was achieved by the combination of a continuous intragastric drip of milk and sodium bicarbonate combined with massive doses of an anticholinergic drug These procedures not only protected the surface of the ulcer from a stimulus adequate to produce pain but also halted the acid pepsin attack upon the tissue allowed the reparative processes of the body to gain dominance decreased the chemical inflammation raised the pain threshold and so rendered the mechanical and chemical factors incapable of producing pain The therapy was continued and with the development of achlorhydria following radiation therapy this non irritative non digestive milieu persisted and the ulcer healed

## THE DIFFERENTIAL DIAGNOSIS OF *BENIGN AND MALIGNANT GASTRIC ULCER*

The old argument with respect to carcinomatous transformation of benign ulcer has long been superseded by the problem of the differentiation of the two lesions—benign ulcer versus peptic ulceration in neoplasm masquerading as benign ulcer (33 34) There are no pathognomonic signs of benignancy The prevailing surgical viewpoint is that all gastric ulcers should be resected This conclusion has never seemed to us to be justifiable and as the passing years bring refinement of technics and new methods of study the policy becomes less and less defensible In 1954 using methods available prior to that time Levin *et al* (35) reported a diagnostic accuracy in benign ulcer of 95 9 per cent A review of 1 000 cases at the Lahey Clinic revealed that death in unoperated patients from cancer of the stomach which had been diagnosed as benign ulcer was 1 7 per cent (Smith Boles and Jordan 36) The same study listed the operative mortality in patients undergoing resection for benign ulcer as 4 85 per cent Dworken Roth and Duber (37) made a follow up study of 135 patients diagnosed as having benign ulcer between 1916 and 1953 Adequate data were obtained in 130 (96 4 per cent) Four cancers were found two at operations performed because of failure to heal the other two patients had been discharged from the hospital before radiologic evidence of heal

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X RAY

The accuracy of the roentgenologic examination is to some extent a function of the experience of the radiologist and the equipment at his disposal Surprisingly different figures have been reported Dagradi and Johnson (38) for instance assign to the method a diagnostic accuracy of only 47 7 per cent whereas Klotz *et al* (39) reported an accuracy of 88 per cent in the diagnosis of 82 surgically proved gastric neoplasms and an accuracy of 79 per cent in the diagnosis of 122 benign gastric ulcers The importance of fluoroscopy and of mucosal relief views should be emphasized for they help greatly in understanding the amount and type of infiltration into the wall surrounding the ulcer The diagnostic accuracy is further improved when comparative views of the ulcer are obtained at intervals of two to four weeks Malignant ulcers rarely heal neoplastic infiltration of the wall at the site of the scar can usually be detected radiologically (34) When the gastric folds radiate to a central point with no evidence of infiltration of the mucosa or of the gastric wall (see Fig 3) the benignancy of the process is almost certain (3 28)

GASTROSCOPY

Just as the roentgenologic method is to a considerable extent a function of the skill and experience of the examiner so too is the gastroscopic method largely dependent upon the examiner A disadvantage of the method is the fact that too often the lesion lies in a gastroscopic blind area In spite of this Klotz *et al* (39) obtained a diagnostic accuracy of 80 per cent in the 82 surgically proved neoplasms and of 80 per cent in their 122 benign gastric ulcers 96 of the latter had been visualized at gastroscopy and with one exception interpreted correctly Thus when the ulcer and its surrounding mucosa are visualized the experienced gastroscopist can be of great help in the differentiation of the two lesions The diagnostic accuracy if the ulcer is visualized should exceed 85 per cent Objective evidence of healing of the ulcer with the demonstration of mucosa not infiltrated with neoplasm should bring the accuracy of the procedure close to 100 per cent

EXFOLIATIVE CYTOLOGY

An additional diagnostic method which is proving to be increasingly accurate and reliable is the examination of the gastric content for neoplastic cells The procedure must be carried out under proper conditions and by experienced personnel Ross *et al* (40) in their first 41 patients with proved gastric cancer found the cells in the gastric content of 71 per cent in 151 patients with benign lesions the authors report one error

occurring in a patient with gastric polyposis The recovery of individual or even small clusters of malignant cells under such circumstances is quite conceivable even though frank carcinoma was not found serial sections may disclose carcinoma *in situ* In the initial years of gastric cytology in our laboratory the accuracy of the method was about 77 per cent it has since risen to over 90 per cent In 131 consecutive cases of proved malignancy examined in the past three years cancer cells were demonstrated preoperatively in 95 per cent in the last 99 cases of operatively proved benign ulcer the procedure was negative in 99 per cent the one error was due to the failure to distinguish actively regenerating mucosal cells

## THERAPY

The basic principles of therapy are old they are outlined by Dr Kirsner in detail in chapter 6 of this volume and relate to methods which decrease gastric secretion by means of anticholinergic drugs or neutralize the acid by means of frequent feedings and antacids (44) Rest is always most important The *success of this program depends upon the patient* his personality "life situation" and other diseases present as well as certain pathologic features such as the presence of pyloric obstruction or gastric retention or chronic perforation of the ulcer into the capsule of the pancreas or liver Finally the skill perseverance and tact of the physician are *vital factors* It is apparent therefore that the choice of treatment and the details of therapy will depend upon the circumstances present in the individual case

Since the one requisite for chronic gastric ulcer is the presence of free hydrochloric acid and peptic activity the conclusion follows that continued achlorhydria would permit the ulcer to heal and remain healed The four cases presented illustrate the validity of this concept the ulcers healed and have remained healed to date achlorhydria having persisted for known periods of two six and twelve years with a recurrence of minimal secretion in patient D M after eighteen months (Figs 3-8 Tables 1 and 2)

A previous study (35) in which 41 patients developed postradiation achlorhydria revealed that healing of the ulcer occurred in the 40 whose achlorhydria lasted for three months or more In no instance did the ulcer recur during the period of histamine fast achlorhydria Lest one draw the erroneous conclusion from these cases that radiation therapy is the ideal treatment for peptic ulcer it should be noted that a total of 116 patients with gastric ulcer were treated in the study cited achlorhydria developed in only 41 The incidence is even lower in duodenal ulcer Consequently even though the results of radiation therapy in such cases as those pre

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inability to maintain an intragastric pH above 5 The clinical manifestations requiring surgery are failure of the ulcer to heal prompt recurrence of the lesion retention with or without nausea and vomiting and uncontrollable bleeding The preferred procedure is usually subtotal resection of the stomach although in thin nervous patients particularly women the so called **postgastrectomy state**, with the dumping syndrome and extreme malnutrition may be much more disabling than the original ulcer Consequently judgment and individualization of procedures are as necessary in the choice of surgical therapy as they are in the medical program

## SUMMARY

The essential role of free hydrochloric acid and peptic activity in the pathogenesis pain and course of gastric ulcer is reviewed and illustrated with four selected case reports The average secretory level does not exceed the mean for normal individuals The important facts are that the mucosa is able to secrete free hydrochloric acid and that peptic activity is present The relationships between acid pepsin attack mucosal resistance or susceptibility chemical inflammation pain threshold stimuli for the production of pain and the course of the lesion are elucidated The invariable disappearance of pain healing of the ulcer and persistence of healing during histamine proved achlorhydria of three months or longer constitute proof of the concepts presented

The criteria for differentiating benign from malignant ulcer are described The significance of the history physical examination gastric analysis fecal examination for occult blood roentgenologic study gastroscopy and exfoliative cytology are considered with the conclusion that the combined diagnostic procedures should yield an accuracy of over 98 per cent

The basic principles of therapy derive from the role of acid gastric juice and peptic activity in the pathogenesis of the lesion Rest psychotherapy and the doctor patient relationship are all important in the application of these principles Complications such as gastric retention with or without pyloric obstruction uncontrollable or repeated massive hemorrhage and failure of the ulcer to heal or to remain healed may constitute indications for surgical interference

## CONCLUSIONS

1 Acid gastric juice and peptic activity are essential for the formation and persistence of a chronic gastric ulcer
2 The chemical inflammation in and about the ulcer lowers the visceral pain threshold so that chemical (acid) and mechanical (peristalsis spasm tension pressure) stimuli become adequate to evoke pain

sented in this chapter are most dramatic the procedure must be looked upon as an adjunct to the total treatment of the patient (46 47)

It is appropriate to ask How successful is the medical therapy of gastric ulcer?

An analysis of the results of therapy in the 116 patient series mentioned above is as follows

| | |
|---|---|
| Favorable results | 80 patients (69 per cent) |
| Failure to heal | 8 patients (7 per cent) |
| Recurrences | 28 patients (24 per cent) |

A total of 108 patients in the series of 116 did receive relief from pain and healing of their ulcers on an adequate therapeutic regimen but the greater

TABLE 3

CAUSES OF DEATH IN 25 MEDICAL MANAGEMENT PATIENTS

(Series of 116 Patients)

| Cause of Death | Number of Patients | Years after Therapy |
|---|---|---|
| Cardiovascular disease | 12 | 1–12 |
| Carcinoma | | |
| Pancreas | 3 | 1–13 |
| Right lung | 2 | 7 and 13 |
| Site unknown | 1 | 4 |
| Prostate | 1 | 9 |
| Perforated ulcer | 1 | 13 |
| Tuberculosis | 1 | 6 |
| Diabetes with complications | 1 | 10 |
| Suicide | 2 | 6 and 8 |
| Homicide | 1 | 2 |

problem is preventing recurrence Although a great many patients remained free of symptoms—49 of the 80 successful cases had been ulcer free for five years or more at the time of follow up—others in the series of 116 suffered recurrences Patients grow weary of the diet and frequent feedings the antacids and other medication consequently they follow the programs with varying degrees of faithfulness

The follow up study (35) made in 1954 revealed that of the 116 patients treated between 1937 and 1954 91 were still living Table 3 shows that only one death could be directly attributable to ulcer disease

Thirty of the 116 patients (26 per cent) eventually came to surgery In medical management cases indications for operation derive primarily from failure of the ulcer to heal or remain healed The most common cause of therapeutic failure is a combination of gastric retention plus an

inability to maintain an intragastric pH above 5 The clinical manifestations requiring surgery are failure of the ulcer to heal prompt recurrence of the lesion retention with or without nausea and vomiting and uncontrollable bleeding The preferred procedure is usually subtotal resection of the stomach although in thin nervous patients particularly women the so called **postgastrectomy state,** with the dumping syndrome and extreme malnutrition may be much more disabling than the original ulcer Consequently judgment and individualization of procedures are as necessary in the choice of surgical therapy as they are in the medical program

## SUMMARY

The essential role of free hydrochloric acid and peptic activity in the pathogenesis pain and course of gastric ulcer is reviewed and illustrated with four selected case reports The average secretory level does not exceed the mean for normal individuals The important facts are that the mucosa is able to secrete free hydrochloric acid and that peptic activity is present The relationships between acid pepsin attack mucosal resistance or susceptibility chemical inflammation pain threshold stimuli for the production of pain and the course of the lesion are elucidated The invariable disappearance of pain healing of the ulcer and persistence of healing during histamine proved achlorhydria of three months or longer constitute proof of the concepts presented

The criteria for differentiating benign from malignant ulcer are described The significance of the history physical examination gastric analysis fecal examination for occult blood roentgenologic study gastroscopy and exfoliative cytology are considered, with the conclusion that the combined diagnostic procedures should yield an accuracy of over 98 per cent

The basic principles of therapy derive from the role of acid gastric juice and peptic activity in the pathogenesis of the lesion Rest psychotherapy and the doctor patient relationship are all important in the application of these principles Complications such as gastric retention with or without pyloric obstruction uncontrollable or repeated massive hemorrhage and failure of the ulcer to heal or to remain healed may constitute indications for surgical interference

## CONCLUSIONS

1 Acid gastric juice and peptic activity are essential for the formation and persistence of a chronic gastric ulcer
2 The chemical inflammation in and about the ulcer lowers the visceral pain threshold so that chemical (acid) and mechanical (peristalsis spasm tension pressure) stimuli become adequate to evoke pain

sented in this chapter are most dramatic, the procedure must be looked upon as an adjunct to the total treatment of the patient (46, 47).

It is appropriate to ask: How successful is the medical therapy of gastric ulcer?

An analysis of the *results of therapy in the 116 patient series mentioned* above is as follows:

| | |
|---|---|
| Favorable results | 80 patients (69 per cent) |
| Failure to heal | 8 patients (7 per cent) |
| Recurrences | 28 patients (24 per cent) |

A total of 108 patients in the series of 116 did receive relief from pain and healing of their ulcers on an adequate therapeutic regimen, but the greater

TABLE 3

CAUSES OF DEATH IN 25 MEDICAL MANAGEMENT PATIENTS

(Series of 116 Patients)

| Cause of Death | Number of Patients | Year after Therapy |
|---|---|---|
| Cardiovascular disease | 12 | 1–12 |
| Carcinoma | | |
| Pancreas | 3 | 1–13 |
| Right lung | 2 | 7 and 13 |
| Site unknown | 1 | 4 |
| Prostate | 1 | 9 |
| Perforated ulcer | 1 | 13 |
| Tuberculosis | 1 | 6 |
| Diabetes with complications | 1 | 10 |
| Suicide | 2 | 6 and 8 |
| Homicide | 1 | 2 |

problem is preventing recurrence. Although a great many patients remained free of symptoms—49 of the 80 successful cases had been ulcer free for five years or more at the time of follow-up—others in the series of 116 suffered recurrences. Patients grow weary of the diet and frequent feedings, the antacids and other medication; consequently, they follow *the programs with varying degrees of faithfulness.*

The follow-up study (35) made in 1954 revealed that of the 116 patients treated between 1937 and 1954, 91 were still living. Table 3 shows that only one death could be directly attributable to ulcer disease.

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3 Peptic digestion in cancer is primarily responsible for the chief problem in differential diagnosis Nevertheless using the available modern diagnostic procedures the accuracy of differentiation between benign and malignant gastric ulcer should be greater than 98 per cent

4 Therapy should be directed toward inhibition of gastric digestion The details depend upon a variety of factors in the individual patient

## ACKNOWLEDGMENTS

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JOHN H LANDOR

# 10 *Small Ulcerative Lesions in the Stomach Benign or Malignant?*

The problems of diagnosis and therapy in patients with gastric ulcer have engaged the attention of internists and surgeons for many decades Although there is almost universal agreement that the patient with obstruction acute perforation uncontrollable hemorrhage or obvious malignant ulcer is primarily a surgical problem there is no unanimity of opinion concerning the management of patients who do not fall into these categories Between the two extremes—that which advocates prolonged, intensive medical therapy and the other which favors immediate surgery—are a large number of clinicians who recommend varying periods of trial on medical management as a first step to see if the ulcer will heal

Some questions which seem pertinent in attempting to resolve the conflict are the following How many gastric carcinomas will be overlooked if all patients with gastric ulcer are treated medically? If a malignant ulcer is treated medically because of erroneous diagnosis will the chances for surgical cure be lessened by the delay? How does the mortality rate following surgical treatment compare with the mortality rate in medical treatment? How accurate are the diagnostic means available for differentiating benign from malignant ulcer? How does the incidence of recurrent ulceration and its complications in the medically treated patient compare with the incidence of adverse effects from gastrectomy in the surgically treated patient?

Unfortunately sound scientific answers to these questions are not forthcoming in spite of voluminous literature on the subject This is un

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derstandable in part because changing methods of diagnosis and therapy make it difficult to approach the problems today if judgment is based entirely on results collected five ten fifteen or more years ago It is also difficult to apply the experience compiled at one institution toward the problem as it may exist in another institution there may be wide differences in the availability of various diagnostic techniques as well as in the quality of either medical or surgical therapy The reliability of the data and how well they are reported are additional factors

With these problems in mind a study was made of patients who had undergone surgery at the University of Chicago Clinics It is beyond the scope of this paper to attempt to resolve completely these questions about diagnosis and therapy in the patient with gastric ulcer However it is hoped that the material contained herein will help to clarify some aspects of the more perplexing clinical problems

## BENIGN GASTRIC ULCER CLINICAL DATA

No discussion of a particular disease can be complete without some reference to etiology since a knowledge of etiology and pathogenesis is essential for a rational approach to therapy Evidence which incriminates the gastric antrum as an important factor in the cause of benign gastric ulcer is presented in chapters 2 3 and 4 of this volume Clinical and experimental findings strongly suggest that gastric ulcer results when hyperfunction or dysfunction of the antrum leads to a marked increase in the gastric phase of secretion Although ultimate proof of this hypothesis must await further studies it is consistent with the observation that partial or subtotal gastrectomy provided it includes resection of the antrum is followed by a recurrence rate of gastric ulcer that is close to zero Gastrojejunal ulceration following this operation in patients with gastric ulcer is exceedingly rare

The present study consists of a summary of all patients who underwent gastrectomy for benign gastric ulcer at Chicago from 1951 through 1957 as well as those with small ulcerating carcinomas who came to surgery during the same period of time These cases represent the efforts of the resident staff as well as those of the entire attending staff Patients with pyloric channel ulcer were omitted from the study because this type of ulcer is believed by many including the author to be more closely related to duodenal ulcer than to gastric ulcer The much larger number of patients with non ulcerative carcinoma of the stomach and those with large malignant ulcers which did not resemble benign gastric ulcers were also excluded

During the seven year period covered a total of 71 patients underwent gastrectomy for benign gastric ulcer In 5 of these patients vagotomy was

done in addition to partial or subtotal gastrectomy either because the fasting acid secretion was higher than normal or because there was evidence of a pre existing duodenal ulcer or both The factors of age sex level of gastric acidity and presence or absence of occult blood in the tools will not be analyzed because large bodies of evidence show that none of these can be relied upon to differentiate between benign and malignant ulcer of the stomach Although histamine achlorhydria and the persistence of occult blood in the stools are highly suggestive of malignancy an occasional benign gastric ulcer patient will have one or two histamine tests which fail to reveal any free acid and there may be some evidence of bleeding for several weeks after intense medical treatment is instituted There are also of course those patients with carcinoma of the stomach who have a normal or high secretion of free acid and who give no evidence of gastrointestinal bleeding

It is convenient to classify this series of 71 patients into three groups

**Group 1** consisted of 2 patients whose preoperative examinations suggested malignant gastric ulcer but pathologic study of the resected specimens disclosed benign ulcers At the time of operation the surgeon was of the opinion in each case that he was dealing with an ulcerated neoplasm therefore the design of the operations was for cancer of the stomach rather than for treatment of gastric ulcer

**Group 2** consisted of 10 patients in whom surgery was performed for the control of hemorrhage which had failed to respond otherwise The majority of these patients had been on medical management for benign gastric ulcer for varying periods of time prior to the bleeding episode

**Group 3** consisted of 59 patients in whom subtotal gastrectomy was performed for uncomplicated benign gastric ulcer Although there was suspicion of malignancy in some of these cases pathologic examination revealed benign ulcer in all cases

RELIABILITY OF DIAGNOSTIC MEASURES

*X ray examination*—Of the 71 patients operated for benign gastric ulcer 69 had undergone at least one gastroduodenal X ray examination The diagnostic impressions of the radiologist are given in Table 1 An unequivocal diagnosis of benign ulcer was made in 50 patients (72 5 per cent) Question was raised as to the benignancy or malignancy of the ulcer in 9 patients and the impression was that of malignant ulcer in 6 The most important fact is that the lesion was missed in only 4 patients (5 8 per cent)

*Gastroscopy*—Thirty nine of the 71 patients in this series were subjected to at least one gastroscopy Table 2 lists the results of these examinations In 16 of the 39 patients the gastroscopist either could not see the lesion or could not obtain an adequate examination of the stomach to express an

opinion Eighteen of the remaining 23 patients were diagnosed correctly in 3 cases benign ulcers were thought to be malignant and the possibility of malignancy was raised in the other 2 patients

*Gastric cytology* —Exfoliative cytology was employed in 33 of the 71 patients The results are shown in Table 3 By this technic a high degree of diagnostic accuracy was achieved as is obvious in the fact that only

TABLE 1

X RAY DIAGNOSIS PRIOR TO SURGICAL PROOF OF BENIGN GASTRIC ULCER

(69 patients)

| X ray Impressions | Number of Patients |
|---|---|
| Benign ulcer | 50 (72 5 per cent) |
| Probably benign ulcer | 4 (5 8 per cent) |
| Possibly malignant ulcer | 5 (7 2 per cent) |
| Malignant ulcer | 6 (8 7 per cent) |
| No lesion seen | 4 (5 8 per cent) |

TABLE 2

GASTROSCOPIC RESULTS PRIOR TO SURGICALLY PROVED BENIGN GASTRIC ULCER

(39 cases)

| Gastroscopic Impressions | Number of Patients |
|---|---|
| Benign ulcer | 18 (46 2 per cent) |
| Possibly malignant ulcer | 2 (5 1 per cent) |
| Malignant ulcer | 3 (7 7 per cent) |
| *Unsatisfactory* examination or failure to visualize ulcer | 16 (41 per cent) |

TABLE 3

RESULTS OF GASTRIC EXFOLIATIVE CYTOLOGY IN SURGICALLY PROVED BENIGN GASTRIC ULCER

(33 patients)

| Cytology Report | Number of Patients |
|---|---|
| Negative for malignant cells | 29 (87 9 per cent) |
| Equivocal | 3 (9 1 per cent) |
| Malignant cells reported | 1 (3 0 per cent) |

one false positive result was obtained There were three instances in which malignancy could not be ruled out because of the presence of some atypical cells

RESULTS OF SURGICAL TREATMENT

*Surgical mortality* —In Group 1 with a presumptive diagnosis of carcinoma in both patients and no evidence of metastases a curative cancer operation was attempted in each instance One patient had a thoracolap

arotomy with total gastrectomy and splenectomy the other had a subtotal gastrectomy splenectomy and partial pancreatectomy for posterior penetrating ulcer Both patients died of postoperative complications a mortality rate of 100 per cent in this group with erroneous diagnosis (Table 4)

Among the 10 patients in Group 2—those with hemorrhage as a complication—three deaths occurred following gastrectomy giving a mortality rate of 30 per cent One of these patients gave a history of angina pectoris which was aggravated by his episodes of bleeding Surgery was performed for continued vigorous bleeding and the patient died in shock on the first postoperative day Cause of death could not be determined Prior to operation the second patient had received twenty eight blood transfusions and had developed an aspiration pneumonitis The pneumonitis became

TABLE 4

OPERATIVE MORTALITY AFTER GASTRECTOMY FOR BENIGN GASTRIC ULCER

| Group | Number of Patients | Deaths | Per Cent |
|---|---|---|---|
| Total series | 71 | 5 | 7 |
| Group 1 patients with erroneous diagnosis of carcinoma | 2 | 2 | 100 |
| Group 2 patients with uncontrolled hemorrhage | 10 | 3 | 30 |
| Group 3 patients electing surgery for benign ulcer | 59 | 0 | 0 |

more severe following surgery and was presumably the immediate cause of death The third patient was diabetic with pulmonary emphysema and cor pulmonale He was operated on reluctantly because of intractable hemorrhage and he died early in the postoperative period Autopsy revealed the most likely cause of death to be acute congestive failure

There was no surgical mortality among the 59 patients in Group 3 who were subjected to subtotal gastrectomy for benign and uncomplicated gastric ulcer

FOLLOW UP STUDIES

Of the 66 patients who survived operation for benign gastric ulcer all but one were examined subsequently to determine the results of the operation Two patients died of carcinoma of the lung five months and sixteen months after surgery but they had obtained good results from the surgery performed for their gastric ulcer The follow up studies on the remaining 63 patients covered periods from several months to six years averaging

18 4 months for the entire group It is apparent that this is not long enough for the development of final results However since recurrent or stomal ulcer is rare in gastric ulcer patients the failures are probably direct consequences of the surgical procedure itself Complaints such as the dumping syndrome and symptoms due to the small residual stomach usually manifest themselves early in the postoperative course and tend to diminish with the passage of time Therefore even though the follow up period is short in some patients the information should closely approximate long term results with the possible exception of recurrent ulceration

The results of operation as shown in Table 5 divide the patients into

TABLE 5

RESULTS OF OPERATION FOR BENIGN GASTRIC ULCER

(Follow up in 63 patients)*

| R lt | Number of Pat ts |
|---|---|
| Good | 53 (84 1 per cent) |
| Fair | 9 (14 3 per cent) |
| Poor | 1 (1 6 per cent) |

* Of th 71 pat ts i th se es 5 d ed po t pe t ly 2 d ed l t f m l ted a d 1 w lost t f ll w up

three categories Good results were enjoyed by 53 of the 63 survivors on whom follow up data were obtained these 53 patients returned to normal full time activities with no troublesome symptoms Nine patients showed fair results they returned to full time activity but were troubled by occasional symptoms requiring changes in diet or periods of medical treatment The only patient who suffered poor results continued to have gastrointestinal symptoms which necessitated almost constant management by diet and medication

## THE SMALL MALIGNANT GASTRIC ULCER CLINICAL DATA

In addition to the above series of 71 patients there were 21 patients with small gastric ulcers which proved to be malignant operations were performed on them during this same period (1951 through 1957) None of these 21 patients had frank evidence of carcinoma when they entered the University of Chicago Clinics Six were first seen by surgical services and 15 were first seen by the medical services and later referred for operation All of the surgical patients came to operation within a month of their initial visit Six of the fifteen medical patients were referred for operation within the first month while the remaining nine patients were treated medically for presumed benign gastric ulcer for periods of time ranging

from six weeks to fourteen months The average length of medical treatment in this latter group was seven months

RELIABILITY OF DIAGNOSTIC MEASURES

In tabulating the results of the three principal diagnostic examinations utilized only the first of each type of examination is reported In several instances a repeat examination later in the course of the patient s illness gave evidence of malignancy whereas the initial such examination had been negative in this respect However it is believed that these first examinations are the crucial ones for if negative they may lull the clinician into a false sense of security

TABLE 6

INITIAL X RAY DIAGNOSIS PRIOR TO PROVED MALIGNANT GASTRIC ULCER

(20 patients)

| X ray Diagnosis | Number of Patients |
|---|---|
| Benign ulcer | 12 (60 per cent) |
| Probably benign ulcer | 1 (5 per cent) |
| Possibly malignant ulcer | 4 (20 per cent) |
| Malignant ulcer | 1 (5 per cent) |
| No lesion seen | 2 (10 per cent) |

TABLE 7

INITIAL GASTROSCOPIC IMPRESSION PRIOR TO PROOF OF MALIGNANT GASTRIC ULCER

(15 patients)

| Gastroscopic Impression | Number of Patients |
|---|---|
| Unsatisfactory examination or failure to visualize ulcer | 4 (26 7 per cent) |
| Benign ulcer | 6 (40 0 per cent) |
| Malignant ulcer | 3 (20 0 per cent) |
| Equivocal | 2 (13 3 per cent) |

*X ray examination* —All but one of the 21 patients with malignant gastric ulcer in this series underwent gastroduodenal X ray examination at the University of Chicago Clinics 12 were diagnosed preoperatively as having benign ulcers In one additional instance the ulcer was felt to be probably benign and four were suspicious enough for the roentgenologist to call them possible malignant Only one ulcer was correctly diagnosed as malignant In 2 of the 20 patients no lesion was seen in the stomach A summary of these initial X ray findings is shown in Table 6

*Gastroscopy* —The impressions of the gastroscopists at the initial examination of the 15 patients who were subjected to gastroscopy are given in Table 7 The lesion was visualized in 11 of these patients a

diagnosis of malignant ulcer was made in 3 others Six ulcers were believed to be benign and in two the diagnosis was equivocal meaning that there were some changes not typical for benign ulcer and carcinoma should be considered

*Gastric cytology* —Exfoliative cytology was done in 17 of the 21 patients in this group In 7 patients malignant cells were found In 3 some atypical cells were seen but the impression of the cytologist was that the ulcer was probably benign An unequivocal diagnosis of benign ulcer was made by the cytologist in the remaining 7 patients These results are summarized in Table 8

RESULTS OF SURGERY FINDINGS AND TREATMENT

In this series of 21 patients subjected to operative surgery for gastric ulcer there was one operative death for a mortality rate of 4 8 per cent In 3 patients the malignant process was so widespread that no attempt at curative surgery was made although a palliative resection was done in 2 of these

TABLE 8

INITIAL GASTRIC EXFOLIATIVE CYTOLOGY BEFORE SURGICAL PROOF OF MALIGNANT GASTRIC ULCER

(17 patients)

| Results of Cytology | Number of Patients |
|---|---|
| Negative for malignant cell | 7 (41 2 per cent) |
| Probably negative | 3 (17 6 per cent) |
| Malignant cells present | 7 (41 2 per cent) |

These patients had been treated medically for six weeks ten months and fourteen months respectively

In the group who survived operation and in which the surgeon felt there was a chance for cure 2 patients died one and two months after operation from causes unrelated to the operation or the carcinoma of the stomach Of the remaining 15 patients 6 have died from recurrence within eight months to four and one half years after resection Average survival time in this group was 24 2 months Nine patients are alive and well with no evidence of recurrent carcinoma from two months to four and one half years later Average period of follow up in those free of disease is 26 2 months It is apparent that many of these patients were operated upon too recently to enable an accurate assessment of long term survival rate

## DISCUSSION

BENIGN GASTRIC ULCER

There are two primary objections to the treatment of benign gastric ulcer by surgical means operative mortality and the disabling symptoms which

occasionally follow gastrectomy Although the over all mortality in this series was 7 per cent there were no operative deaths in those patients who came to resection with the correct preoperative diagnosis and who were not bleeding acutely Mortality figures in other recent and similar series range from 0 to 6 3 per cent (1–9)

Most experienced surgeons achieve the low operative mortality of 1–2 per cent when treating uncomplicated gastric ulcer it seems unlikely that this figure may become much lower in the near future Although any mortality is to be deplored it must be remembered that gastric ulcer itself leads to death in an appreciable number of patients treated medically Thus Swynnerton and Tanner (9) report a 2 7 per cent mortality in 262 patients treated medically and Dworken *et al* (10) report a mortality rate of 3 7 per cent That the patients who are destined to die if treated medically will necessarily be the same patients who die if surgery is decided upon is a problematical and philosophical consideration which we are (perhaps fortunately) in no position to resolve

The occurrence of two deaths in our series following erroneous preoperative and operative diagnosis of ulcerating carcinoma points out the importance of careful and thorough diagnostic work up This is especially true in penetrating gastric ulcer which simulates carcinoma the surgeon feels compelled to remove part of the pancreas or liver when penetration of these organs has occurred if the lesion is thought to be malignant If carcinoma could be ruled out the base of the ulcer and the adjacent organ could be left intact and the operation would entail much less risk

As for the distressing symptoms which occasionally follow gastrectomy it must be remembered that the incidence of disability is far less than the disability incurred from recurrent ulceration and its complications in patients treated solely by medical means Only 1 patient in this series of 63 who survived gastrectomy for benign gastric ulcer experienced disabling symptoms This is similar to the surgical experience of others Welch and Allen (5) report that 75 per cent of their surgical series were asymptomatic 15 per cent had mild symptoms and another 10 per cent had severe symptoms Swynnerton and Tanner (9) had results which were 80 per cent very satisfactory 10 per cent satisfactory 7 4 per cent fairly satisfactory and 5 9 per cent unsatisfactory

On the other hand among those patients treated medically the recurrence rate of gastric ulcer is generally high Eleven to 43 per cent have later come to operation because of recurrence or intractability (4 9 10 11 12 13) Levin Palmer and Kirsner (11) reported a recurrence rate of 39 7 per cent Fierst (13) experienced a recurrence rate of 50 per cent that of Swynnerton and Tanner (9) was 76 4 per cent Many of these patients require repeated hospitalizations for intensive therapy of their

gastric ulcers and thereby lose valuable time away from their jobs and families

Another factor to be considered if the decision is made to embark upon medical management is the possibility of the development of serious com plications such as hemorrhage Welch and Allen (5) found that 9 per cent of all benign gastric ulcers seen over a ten year period bled massively The gravity of this complication is made apparent by our operative mortality rate of 30 per cent in the ten patients who came to operation late in the course of an episode of hemorrhage The patient who has bled massively represents a poor operative risk not only because of possible vascular col lapse but also because of the secondary complications particularly aspira tion pneumonitis and atalectasis An additional danger of considerable importance is the increased incidence of renal shut down from hypoten sion and/or whole blood transfusions The risk of homologous serum hepa titis is of course greater with each succeeding unit of blood given These complications are potentially lethal particularly when the patient is al ready debilitated from his primary disease

## CARCINOMA MASQUERADING AS BENIGN GASTRIC ULCER

The question of whether the truly benign gastric ulcer ever becomes malignant is discussed in the preceding chapter in this volume We know of no convincing proof that this phenomenon has occurred although it cannot be completely excluded If such a transition were shown to occur this would provide powerful argument for surgical treatment of all gastric ulcers However disregarding this possibility the fact remains that many gastric lesions which look and act like benign ulcer—even to the point of healing under medical management—are actually neoplasms which have undergone peptic ulceration

The incidence of malignancy in ulcerating lesions of the stomach which appear benign is difficult to determine with the accuracy desired In various surgical series it ranges from 4 per cent to almost 30 per cent (2 5 6 7 12 13 14 15 16) Although these figures are undoubtedly higher than *would be found if all patients with gastric ulcer were considered* regardless of the treatment used it is distressingly obvious that a malignant ulcer can appear to be benign in a significantly high percentage of patients

In our series of malignant ulcers more than half were diagnosed as be nign by the roentgenologist and more than half of those ulcers seen at gastroscopy were interpreted as benign by the gastroscopist This degree of error in diagnosis is understandable since it is a common experience for the surgeon to visualize and palpate an ulcer directly and still not be able to make the correct diagnosis Ravdin and Horn (17) stated that

seven malignant ulcers although correctly diagnosed preoperatively were thought to be benign by the pathologist on gross examination

Exfoliative cytology is a method which holds much promise since it does not depend upon the gross appearance of the lesion Indeed cytologists in this institution have been able to achieve a diagnostic accuracy of approximately 95 per cent in all gastric lesions Unfortunately this has not been true in the case of the small malignant ulcer malignant cells being found in only 7 of 17 cases It is possible that with more experience and refinement in technic this method may provide an accurate means of distinguishing between these difficult lesions in the future Understandably the small lesion will shed fewer cells than the large one and on this basis alone the difficulties can be explained The need for a reliable method of diagnosis can hardly be overemphasized

Accurate diagnostic methods are certainly mandatory if the patient with presumed benign gastric ulcer is to be subjected to medical management for any period of time in excess of a few weeks The best five year survival rates are those obtained in patients with small malignant gastric ulcers provided they are subjected to early surgery Among this group Runyeon and Hoerr (7) had a three to five year survival rate of 46 per cent Lampert *et al* (16) reported a five year survival of 43 5 per cent Ransom (15) a rate of 41.2 per cent In the Olssen and Endresen series (14) 65 per cent of the patients with malignant ulcers with no evidence of lymph node metastases survived at least five years That prompt surgical intervention is necessary in patients with a malignant ulcer is apparent from the report of Hayes (12) who found a five year survival rate of 66 per cent when the operation was performed within four weeks of medical therapy for gastric ulcer This survival rate fell to 43 5 per cent for those in his group who had been treated for more than four weeks and when operation was delayed until definite evidence of carcinoma was present it dropped to 18 per cent Similarly Welch and Allen (5) found a five-year survival rate of 40 per cent in those treated medically for less than one month but no survival for five years in patients treated for six or more months

## CONCLUSION

Current available data including those presented in this report indicate that surgical mortality for the non bleeding benign gastric ulcer is no higher than the mortality incurred by medical therapy in this disease In medical series the recurrence rate of gastric ulcer is sufficiently high that it seems likely the disease causes more disability than the post gastrectomy syndrome in patients treated by gastric resection Since there is at present no highly accurate method for differentiating between benign

and malignant ulcer prolonged medical treatment carries with it a most serious risk—that of dooming a patient to die of a malignant disease which may have been curable in its earlier stages For these reasons the treatment of gastric ulcer appears to be primarily surgical and the vast majority of proved chronic gastric ulcers should receive prompt surgical therapy

## SUMMARY

1 A series of 71 patients with benign gastric ulcer and a series of 21 patients with small malignant gastric ulcer all of whom were subjected to surgical treatment are analyzed with regard to diagnostic and therapeutic problems experienced and end results are obtained

2 In the group of patients with uncomplicated benign gastric ulcer no deaths occurred in 59 who were electively subjected to gastric resection However in the 10 patients with small benign gastric ulcer operated upon for acute hemorrhage 3 died Two patients who were thought to have malignant gastric ulcer succumbed as a result of operation

3 Of the patients who survived operation for benign gastric ulcer 84 1 per cent reported a good result 14 3 per cent a fair result and 1 6 per cent a poor result

4 Among the 21 patients with small malignant ulcer accurate preoperative diagnosis was achieved in less than one half of the patients by X ray gastroscopy or exfoliative cytology

5 These results are discussed along with other relevant and recently published series

This material supports the contention that in the treatment of gastric ulcer the best results are achieved in those patients subjected to early gastrectomy This statement takes into consideration the relative disability from medical and surgical treatment the advantage of early resection should the lesion prove to be malignant upon histologic examination and finally the fact that a significant number of small ulcerative lesions found in the stomach do prove to be malignant

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THE GASTRIC OR ANTRAL SECRETORY PHASE

This phase is distinct and largely independent of the vagal or cephalic influence The gastric phase ordinarily is stimulated by antral distention and alkaline foods Usually the antral stimulus produces a lesser rise in acid secretion than that of vagal stimulation but under certain circumstances its secretory response may equal or exceed that usually encountered when hypersecretion is of vagal or cephalic origin the antral secretory response may dominate The humoral release of gastrin is well supported both by clinical and experimental observations

Thus the effector mechanism in antral stimulation is humoral instead of nervous This agent gastrin has not been identified chemically nor is its origin known Many consider it to be a hormone If this proves to be the case its glandular source remains to be established Its action is not otherwise in conflict with the hormonal concept but until this fact is established the less precise term of a "humoral agent" seems preferable Regardless of its nature gastrin is so intimately associated with the antrum and the release of gastrin is so easily demonstrated in response to antral distention or the presence of alkaline proteins in contact with the mucosal surface of the antrum that its existence and importance to the regulating mechanisms of gastric secretion cannot be seriously questioned

In a sense gastrin may serve to supplement the regulation of the cephalic phase of gastric secretion under normal conditions Since the ingestion of food distends the stomach especially the antrum activating the gastrin mechanism it may very well take over much of the cephalic function when it diminishes after the appetite is satisfied These relationship are worthy of further study which may be expected to yield informative data

Antrectomy as a surgical procedure for the treatment of duodenal ulcer has failed because of the continued function of the cephalic phase and more especially because the vast majority of parietal cells remain intact The tendency in recent years for many surgeons has been to combine antrectomy with vagotomy In this way less of the stomach is removed and both the antral and cephalic phases of secretion are largely abolished Vagotomy with antrectomy (hemigastrectomy) has done much to reduce the mortality of high subtotal gastric resection as well as to make effective

an otherwise inadequate lesser resection. However there is ample evidence that vagotomy coupled with a gastric drainage procedure but without resection is quite sufficient for the surgical treatment of most patients with duodenal ulcers

The close association of gastric retention and gastric ulcer led Dragstedt to postulate that benign gastric ulcer is largely a matter of antral distention and the secretory stimulus this provides for the release of gastrin. Although gastric acidity (concentration of acid) in patients with gastric ulcer may not be greatly elevated, the quantity of acid secreted per unit of time especially during the 12 hour overnight collection is generally above normal in this group of ulcer patients

Considering the importance of antral distention in the activation of the gastrin mechanism, one should expect to find the incidence of gastric ulcer higher in patients who have some degree of gastric retention In spite of the small quantity of clinical evidence in support of this contention a variety of clinical instances suggest that gastric retention is an important factor in the pathogenesis of gastric ulcer Among such occurrences of gastric ulcer we might include the following patients with stenosing ulcer of the duodenum patients in whom vagotomy was carried out previously without a drainage procedure patients whose gastroenterostomy did not provide adequate drainage and those patients reported by Adams and Moulder in whom resection of the gastric cardia with the lower esophagus was carried out for malignancy—surgery which included this portion of the vagus nerves but no drainage procedure Because of gastric retention, the period of exposure to acid pepsin that the gastric mucosa receives is longer in antrally induced hypersecretion In duodenal ulcer gastric motility is often increased so that gastric exposure to hypersecretion may not be much greater than normal In gastric ulcer the stomach is believed to be more vulnerable than the duodenum to the augmented gastric phase of secretion because of the differences in emptying time between duodenal and gastric ulcer In recent years this author has found it helpful to take into consideration the demonstrated presence of gastric retention as *one* of the indices favoring the diagnosis of a benign and high lying gastric ulcer when other criteria do not definitely settle this question

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SPECIAL TYPES OF PEPTIC ULCER

In stress ulcer" in the Zollinger Ellison non insulin producing islet cell tumors of the pancreas in ulcer associated with parathyroid or adrenal adenomata in steroid induced ulcers in Curling's ulcer and that described by Cushing the mediating stimuli may be different from those of chronic peptic ulcer It therefore seems better that these forms of ulcer be considered separately Most of them are acute peptic ulcerations generally they are duodenal though not infrequently they are gastric Despite the apparent benefit of a unitarian view in relation to pathogenesis of peptic ulcer this desire should not obscure the possibility that both the pathologic and physiologic mechanisms in acute peptic ulceration may be different from those of the chronic ulcer—the latter being the central theme of this volume

## PHYSIOLOGY IN PEPTIC ULCER IN RELATION TO SPECIFIC FORMS OF THERAPY

NON SURGICAL TREATMENT OF CHRONIC DUODENAL ULCER

At present medical management and surgical procedures alike can only be directed at the peripheral gastric secretory mechanisms While satisfactory medical and surgical methods for the control of gastric acidity in the treatment of peptic ulcer are well established substantial progress has not been achieved in the more fundamental aspects of stimulated gastric secretion particularly in the elimination of extraneous stimuli favoring hypersecretion when of cephalic origin Until such time that the ulcer problem can be attacked at levels more basic than now possible we must be content to treat the secretory mechanisms vigorously—the stimulated mechanics that create increased gastric secretion and acidity In other words present therapy is directed primarily at the physiologic sequela and not the physiologic stimulus

The variety of methods for the medical management of peptic ulcer attest to some degree of scientific uncertainty Nonetheless most of these yield satisfactory results when properly applied Careful attention to minute details and the vigorous enforcement of the chosen therapeutic regimen are essential to the success of these programs The willingness of the physician to modify his initial program in favor of another should occasion demand is also of therapeutic importance

In principle three features are generally incorporated into the conservative forms of management of duodenal ulcer currently in use Foremost is the neutralization of gastric acidity by the frequent administration of alkaline medications such as are employed in the classical Sippy regime

THE INCREASED NUMBER OF PARIETAL CELLS

Recent reports from several laboratories claim that the number of acid producing parietal cells is increased in patients with duodenal ulcer this constitutes another explanation for the increased acid gastric juice Those reporting this observation contend that it is not necessary to postulate cephalic stimulation in duodenal ulcer Rather they say since there is a greater *number* of parietal cells to respond to the vagus nerve in a normal state of tonus the increase in acid gastric juice which these cells are able to add is sufficient to account for the increased volume of secretion as well as the increase in the quantity of acid observed in patients with duodenal ulcer Stated otherwise hypersecretion of acid gastric juice according to this concept is a quantitative phenomenon the more cells the more acid secreted

Although this thesis is not incompatible with the observed benefits of vagotomy on gastric secretion this suggestion does not account for the increase in *free acid concentration* of the gastric juice of patients with duodenal ulcer An increase in the total *quantity* of acid produced according to this theory is to be expected if the parietal cell increase is functional and therefore important to the regulation of gastric secretion in patients with duodenal ulcer Unless there is little or no increase in the *volume* of gastric juice secreted by these extra cells this thesis will not account for the increased *concentration* of free acid the feature of gastric secretory physiology that is almost universally observed in the duodenal ulcer patient (chaps 1 2 3 and 4) Further there is ample evidence that vagal stimulation by the insulin test increases the quantity of acid to a greater extent than the rise in volume of the juice secreted Similarly many of the classic experiments that produce peptic ulcer in dogs generally disclose the output of acid to exceed that of volume hence the concentration of acid usually is noticeably increased If however the parietal cells are producing acid and the mucous and chief cells are not commensurately increased then concentration of acid should rise for this reason alone

This critique however is not intended to contradict the reported increased numbers of parietal cells in duodenal ulcer patients but simply to point out that hyperplasia" of parietal cells without other changes does not explain the well established increased concentration of free acid that characterizes gastric secretion in these patients In truth the theory of parietal cell hyperplasia is not incompatible with the well established reduction in free acid output following vagotomy

Finally the question of why there is an increase in parietal cells in duodenal ulcer patients needs an answer Is this a response to hypertonia of the vagus nerves or does it occur for some other reason?

often recognized the relief of gastric stasis allowed more effective administration of oral medications How much of the benefit claimed by some for gastroenterostomy was in reality due to more effective subsequent medical management was never satisfactorily established In spite of its *two potential benefits recurrence rates of 30–42 per cent* led to the abandonment of routine gastroenterostomy shortly after 1930

**Antral exclusion operations** were also tested These were devised as simple procedures to exclude acid from the duodenum and to permit the *closure of the distal end of the stomach with greater ease and safety* thereby avoiding the much dreaded blown out duodenal stump that some had experienced when gastric resections were carried just distal to the pylorus However the adverse significance of the retrograde flow of *fluid into the duodenum via the proximal limb of the jejunostomy* and from there into the occluded antrum was not appreciated The antral distention thus created provided the stimulus necessary for the release of gastrin aside from the inadequacy to the resection itself This operation tended to add to the *hypersecretory mechanism of cephalic origin* that of the distended antrum Again the rate of recurrence was higher than could be justified and procedures of this type were generally discontinued

**Higher gastric resection** was the only remaining surgical procedure that seemed rational in the mid 1930s A variety of surgical methods to achieve high resection were advocated to ablate greater portions of the acid secreting fundic and cardiac segments of the stomach The results were gratifying *For the first time recurrence rates of 10 per cent or* slightly less were reported Most agreed that at least a 75 per cent resection of the stomach was necessary to achieve this kind of benefit The high subtotal resection continues to enjoy popularity in many centers today though the *technical aspects may differ considerably from one surgeon to* another

The disadvantages of subtotal gastrectomy were until recently obscured by the enthusiasm for the benefits it achieved The necessity for some patients to eat more frequently and the failure of most to regain their normal weight were indeed small prices to pay for sharp reduction in the recurrence rate considering the many earlier procedures that failed The dumping *syndrome too gained little attention until recent years* Here again dumping was not often so severe as to be disabling or dangerous compared to the similar risks entailed by recurrence especially when complicated by gastroenterocolic fistula or stomal ulceration

**Transthoracic vagotomy** was introduced by Dragstedt in 1943 for the purpose of ablating the effect of the cephalic phase of gastric secretion without resorting to resection His choice of the transthoracic route was to make as certain *as possible that complete division of both vagi was*

The second is directed toward the reduction of gastric secretion belladonna and other drugs with atropine like action have accomplished much to reduce gastric acidity as well as to lessen intestinal motility These "anti secretory drugs have improved considerably the results obtained when neutralization of gastric acidity was the only antacid measure employed Third is the protection of the patient from extraneous stimuli to the extent this may be possible The patient s environmental situation plays an important contributing role in this instance Aside from what may be accomplished by assisting him to reorganize his habits his work diet and similar problems the wise use of mild sedation may be helpful by increasing his threshold to some of the distressful external stimuli to which he may be exposed

In general there is good acceptance of these three therapeutic principles any disagreement which may arise usually centers about differences of opinion as to how best to achieve these goals Fortunately there is considerable latitude and overlap in most forms of ulcer therapy including surgical management Thus the results obtained in one series of patients often can be matched by another s reasonable therapeutic program assuming each program has in common the careful attention of the physician to details and the co operative attitude on the part of the patients comprising the two series As with many chronic diseases recurrences *are not uncommon but in themselves do not constitute reasons for change* or for surgical treatment

SURGICAL THERAPY FOR PEPTIC ULCER

Assuming the standard accepted indications prevail surgery has undergone much greater change during the past sixty years than the programs of medical therapy This is partly due to improvement in technical skill and partly because there is better understanding about what to expect a specific operation to accomplish There continue to be honest differences of opinion which cannot easily be examined on common grounds of experience or of previous orientation and training

**Partial gastric resection for duodenal ulcer** began prior to the turn of this century at a time when surgical procedures of this type carried too high a mortality rate to permit the extent of resection that we now know to be essential for curative relief The result was an early compromise *small resections were performed which carried less risk but* which inevitably led to an intolerably high rate of recurrence

**Gastroenterostomy without resection** evolved because of its simplicity and lower mortality It provided adequate drainage if stenosis was present and thus reduced to some extent the hypersecretory gastric phase caused by antral distention This procedure had another potential merit not

often recognized the relief of gastric stasis allowed more effective administration of oral medications How much of the benefit claimed by some for gastroenterostomy was in reality due to more effective subsequent medical management was never satisfactorily established In spite of its two potential benefits recurrence rates of 30–42 per cent led to the abandonment of routine gastroenterostomy shortly after 1930

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accomplished This was readily demonstrated in most vagotomy patients whose secretory response to the Hollander insulin procedure was profoundly reduced compared with their preoperative responses which served as controls Failures were generally attributed to incompleteness of vagotomy which led to re exploration The second operation was via the less favored transabdominal route since the previous transthoracic procedure usually resulted in scarring such that identity of the vagi by a re exploration through the chest was difficult and uncertain

Re division of the vagi transabdominally proved technically to be more readily feasible than originally believed Further the freeing up of the esophagus from the diaphragmatic hiatus from below allowed the esophagus to be pulled down readily often the site of the transthoracic vagotomy could be inspected with ease Moreover the transabdominal approach provided the opportunity to examine the stomach and duodenum as well as the ulcer bed itself

Disappointingly however the second vagotomy (transabdominal) did not often reduce gastric acidity among many of the patients considered as transthoracic failures at least not to the extent that seemed reasonable to expect *Several possible explanations were examined In a few patients* large branches of undivided vagal nerves were found at the second operation and these were the patients who were benefited most often by re exploration

Because of the disturbance in gastric motility following vagotomy alone transient gastric retention was the rule Belching and diarrhea were common and trying complaints during these early years After a few months however these sequela usually subsided symptomatically Occasionally gastroenterostomy was necessary as a later procedure However to create a drainage procedure as a routine during the early stages of this study would have made difficult if not impossible an evaluation of the effect of vagotomy on gastric secretion and its curative effects upon duodenal ulcer

Once these points were satisfactorily settled two changes in operative technic were introduced Gastroenterostomy became a routine part of the initial vagotomy and the transabdominal approach was adopted abandoning the transthoracic approach *The results continued to approach* those of high subtotal gastrectomy with 10 per cent or slightly lower recurrence rate within five years Mortality and morbidity have generally been higher for resection than for vagotomy recurrence rate may be slightly less for high resection than for vagotomy

## PHYSIOLOGIC BASIS OF GASTRIC ULCER

In 1949 the first patient to undergo vagotomy for *duodenal* ulcer (1943) and in whom the insulin test had remained negative developed a benign

gastric ulcer Because of frequently performed interval studies it was known that this patient suffered gastric distention though the patient himself was symptomatically unaware of this phenomenon The work of Edkins in 1906 on the gastrin mechanism and the antral hypersecretory phase of gastric secretion was recalled and reviewed to determine whether antral function could have contributed to the formation of gastric ulcer in this patient This patient and his gastric ulcer thus served as the spring board for the reinvestigation of the relation of the gastric antrum to the physiology of gastric secretion Aside from confirming Edkins work knowledge about antral function and its stimulation was greatly extended by Dragstedt and his associates both in the laboratory and in studies on patients The outcome was that Dragstedt was able to account not only for one of the causes of vagotomy failure but also to point out a significant difference between the pathogenesis of duodenal and gastric ulcer

The choice between vagotomy with gastroenterostomy and subtotal gastric resection for the surgical treatment of ulcer remains in controversy conditioned largely upon the surgeon s experience and his previous training However the advent of vagotomy served a purpose greater than its therapeutic benefits It aroused an intense interest in gastric secretory physiology among physicians and surgeons alike The importance and significance of the work of Pavlov of Heidenhain and of Edkins in this field have subsequently become well known to most clinicians engaged in gastroenterology

The clinical management of duodenal ulcer during the past decade has been extensively modified especially its surgical management The failures of gastroenterostomy of hemigastrectomy and of the antral exclusion operations for duodenal ulcer are no longer merely empiric as the data accumulate they are more readily understood Many surgeons who continue to choose resection combine this procedure with vagotomy and thereby are able to perform less severe resection Many others elect vagotomy alone with either gastroenterostomy or pyloroplasty as the operation of choice

## PHYSIOLOGIC IMPACT ON ULCER THERAPY

While we may dependably expect further changes in the management of duodenal and gastric ulcer as newer knowledge becomes available we may well ask even now how best we can proceed with the information at hand Perhaps the most difficult task is the simplest one namely to realize that peptic ulcer is a dynamic disease with a great tendency to wax and wane Each patient is a rule unto himself he will respond best if the physician or surgeon tailors the treatment to meet apparent needs and is guided also by the response of the individual patient This is the kind of

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Re division of the vagi transabdominally proved technically to be more readily feasible than originally believed Further the freeing up of the esophagus from the diaphragmatic hiatus from below allowed the esophagus to be pulled down readily often the site of the transthoracic vagotomy could be inspected with ease Moreover the transabdominal approach provided the opportunity to examine the stomach and duodenum as well as the ulcer bed itself

Disappointingly however the second vagotomy (transabdominal) did not often reduce gastric acidity among many of the patients considered as transthoracic failures at least not to the extent that seemed reasonable to expect Several possible explanations were examined In a few patients large branches of undivided vagal nerves were found at the second operation and these were the patients who were benefited most often by re exploration

Because of the disturbance in gastric motility following vagotomy alone transient gastric retention was the rule Belching and diarrhea were common and trying complaints during these early years After a few months however these sequela usually subsided symptomatically Occasionally gastroenterostomy was necessary as a later procedure However to create a drainage procedure as a routine during the early stages of this study would have made difficult if not impossible an evaluation of the effect of vagotomy on gastric secretion and its curative effects upon duodenal ulcer

Once these points were satisfactorily settled two changes in operative technic were introduced Gastroenterostomy became a routine part of the initial vagotomy and the transabdominal approach was adopted abandoning the transthoracic approach The results continued to approach those of high subtotal gastrectomy with 10 per cent or slightly lower recurrence rate within five years Mortality and morbidity have generally been higher for resection than for vagotomy recurrence rate may be slightly less for high resection than for vagotomy

## PHYSIOLOGIC BASIS OF GASTRIC ULCER

In 1949 the first patient to undergo vagotomy for *duodenal* ulcer (1943) and in whom the insulin test had remained negative developed a benign

in the fundus of the stomach and covered with omentum I believe that duodenal ulcers are due to a hypersecretion of gastric juice in the empty stomach dependent upon excessive and abnormal secretory impulses in the vagus nerves These in turn I believe are in some way aroused by the tensions and strain of modern life I would feel greatly relieved during the first five days after the operation when my stomach was being decompressed by the gastrostomy tube if the output of free acid in each twelve hour aspirate was less than 10 or 15 mEq I would feel still better if on the tenth day after the operation the amount of acid in my twelve hour nocturnal secretion was less than 15 mEq I would then have the tube removed if my stomach was now emptying satisfactorily

I would have my nocturnal gastric secretion measured again at the end of six months and also after a year particularly if any ulcer symptoms persisted If the nocturnal secretion was still within normal limits and the stomach emptying satisfactorily I would be comforted in the thought that in all probability I was now cured of my disease If however I had a recurrence of ulcer symptoms and my own experience has indicated that this is usually due to an incomplete vagotomy or to an inadequate drainage operation I should resume medical management Sometimes medical treatment that was inadequate at first becomes sufficient after an incomplete vagotomy indicating that some good was accomplished by the operation If however medical treatment again proved inadequate and further surgery was required I would now choose to have a two thirds gastric resection with reconstruction of my gastrointestinal tract by the Billroth II operation

If I had a gastric ulcer my choice of therapy would be quite different because I am convinced that these lesions are usually due to a hypersecretion of gastric juice of humoral or hormonal origin and the possibility of malignancy would effect all decisions I would place myself in the hands again of a competent internist and I would be considerably relieved if after his careful study and fluoroscopic examination possibly supplemented by a short period of medical management he concluded that my ulcer was benign I would be still further relieved if exfoliative cytology failed to reveal the presence of malignant cells I am uncertain as to whether or not I would subject myself to a gastroscopic examination If after a period of three or four months of medical management I was still not free of symptoms my anxiety would return that the lesion might be a carcinoma If the ulcer is located in the lower half of the stomach I would elect to have a subtotal gastric resection with reconstruction by the Billroth I method if possible If subsequent examination of the lesion indicated that it was benign I would feel greatly relieved since the development of marginal ulcer after resection of the lower part of the stomach for gastric ulcer is very rare If examination proved the lesion to be a carcinoma I would realize that something although perhaps not very much had been done for me in the way of therapy

If the ulcer is in the upper half of the stomach and within a centimeter or two of esophagus the problem is quite different At operation I would request the surgeon to open my stomach and inspect the lesion if at all possible I should like him to palpate the ulcer with his bare finger and take a biopsy of a suspicious

judgment that is difficult to translate into words because successful treat ment does depend upon full use of all available knowledge and tempered experience

Since this volume is dedicated to Dr Lester R Dragstedt and prepared without his prior knowledge by the Surgical Staff his associates and his former students at the University of Chicago it seems appropriate to re print the following tract in which his own views on the dynamic manage ment of peptic ulcer are clearly stated It emphasizes the need for con sideration of the totality of the ulcer problem in patients with peptic ulcer disease

## WHAT WOULD I DO IF I HAD AN ULCER?"*

BY LESTER R DRAGSTEDT M D

Sometimes it is of value for a surgeon to ask himself just what he would do if he had the lesion that he has found in his patient and had available medical and sur gical care of the same competence Some reflection on this problem has prompted me to write this comment

If I had a duodenal ulcer I would place myself in the hands of a competent in ternist preferably one with a special interest in gastrointestinal diseases I would follow his prescribed management and exercise all of the self discipline in this connection that I could muster If he did not make quantitative measurements of my fasting nocturnal gastric secretion I would request that this determination be done If I discovered that my stomach secreted in excess of 75 mEq of free hydrochloric acid in a twelve hour period as compared with the normal 15 to 20 I would conclude that my problem was a serious one and that medical manage ment might well prove inadequate If my physician did not prescribe neutral ization therapy during the night I believe that I would set my alarm clock to awaken me at the period of maximum secretion when I would partake of a mix ture of milk and cream with some calcium carbonate I would continue with medical management for at least a year unless some serious complication de veloped If at the end of this time I found that I was still handicapped by my disease was less efficient in my work and had to deny myself too much of the pleasures of life I would then seek surgical treatment Since it is my own stomach that we are considering now I would select first that type of surgery which carried the least hazard involved the least mutilation and still provided a good chance to be free of my disease I would choose to have a supradiaphragmatic vagotomy by the abdominal route combined with the posterior gastroenterostomy with a stoma not larger than two centimeters in diameter and located within seven centimeters of the pylorus I would beg the surgeon to make a meticulous dissection of the lower two inches of my esophagus in an effort to make sure that all vagus fibers were divided I would also request him to decompress my stomach for the first five days after the operation by means of a gastrostomy tube placed

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nodular area In the absence of histological proof that the ulcer is a carcinoma I would not wish to have a cancer operation which in this case would mean a total gastrectomy probably with a laparothoracotomy incision Such an operation is too hazardous and the morbidity too great for non malignant disease A removal of the antrum of the stomach leaving the ulcer in situ would remove the humoral phase of secretion and in all probability permit the ulcer to heal The experience with the Kelling Madlener procedure has been most reassuring and physiological studies support this belief

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